Supreme Court of the United States

OCTOBER TERM, 1968

No. 343

UNITED STATES OF AMERICA,

Petitioner,

—v.—

AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * *

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT

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DOCKET ENTRIES IN DISTRICT COURT

DATE	PROCEEDINGS
1962	
May 25.	Libel filed—Monition and attachment issued.
May 29.	Affidavit of mailing filed.
June 5.	Monition and attachment filed.
Aug. 14.	Claim of Difco Laboratories, Inc. filed.
Oct. 22.	Answer of Difco Laboratories, Inc. filed.
1963	
May 2.	Libelant's interrogatories filed.
June 10.	Answer to libelant's interrogatories filed.
June 25.	Appearance filed.
June 25.	Claimant's requests for admissions filed.
July 25.	Answer to claimant's requests for admissions filed, with proof of service.
Nov. 7.	Notice of pre-trial for Nov. 25/63 filed.
Nov. 25.	Pre-trial adj. to Dec. 2/63; Thornton, J.
Dec. 2.	Pre-trial had; Thornton, J.
Dec. 11.	Amended answer filed.
1964	
Apr. 22.	Libelant's motion for summary judgment filed; hearing May 4/64.
May 25.	Motion for summary judgment adj. to June 15/64; Thornton, J.
June 15.	Motion for summary judgment adj. to Aug. 31/64; Thornton, J.
Aug. 19.	Affidavit of Lloyd C. Miller filed.
Aug. 19.	Affidavit of Chester S. Keefer filed.
Aug. 19.	Affidavit of Edward G. Feldmann filed.
Aug. 19.	Affidavit of Arthur C. DeGraff filed.
Aug. 31.	Motion for summary judgment adj. to Sept. 14/64; Thornton, J.
Sept. 10.	Affidavit of William W. Wright, PhD. filed.
Sept. 14.	Libelant's motion for summary judgment heard and taken under advisement; Thornton, J.
Sept. 29.	Affidavit of C. W. Christensen filed.

DATE	PROCEEDINGS
1964	
Sept. 29.	Affidavit of Chester S. Keefer filed.
Oct. 21.	Affidavit of William W. Wright filed.
Oct. 21.	Affidavit of Dr. E. L. Quinn filed.
Oct. 21.	Affidavit of Joseph E. Truant, PhD. filed.
Dec. 30.	Transcript of Sept. 14/64 filed.
1965	
Apr. 6.	Order denying motion for summary judgment filed and entered; Thornton, J.
Apr. 6.	Proof of mailing filed.
Apr. 8.	Notice of trial for May 18/65 filed.
May 11.	Motion for rehearing of libelant's motion for summary judgment filed; hearing May 17/65.
May 12.	Proof of service filed.
May 18.	Trial by court begins—adj. to May 19/65; Thornton, J.
Apr. 19.	Trial by court resumed—adj. to May 20/65; Thornton, J.
Apr. 20.	Trial by court resumed and concluded—matter taken under advisement; Thornton, J.
1966	
July 21.	Memorandum opinion filed and entered; Thornton, J.
July 21.	Proof of mailing filed.
Aug. 31.	Findings of fact and conclusions of law dismissing case with prejudice and that the articles seized and attached be returned to claimant Difco Laboratories (see order), filed and entered; Thornton, J.
Aug. 31.	Proof of mailing filed.
Sept. 1.	Notice of entry mailed.
Sept. 12.	Stay of execution of Decree (60 days from date of entry) filed and entered; Thornton, J.
Oct. 21.	Notice of appeal of United States of America filed.

DOCKET ENTRIES IN COURT OF APPEALS

DATE	PROCEEDINGS
1966	
Oct. 31.	Letter to attorneys re: appeal filed.
Oct. 31.	Proof of mailing filed.
Nov. 16.	Transcript commencing May 18/65 filed.
Nov. 29.	Stipulation as to record on appeal filed.
Nov. 30.	Certified record (1 vol. pleadings and transcript), filed; and cause docketed
Dec. 7.	Appearance of counsel for Appellee
Dec. 8.	Appearance of counsel for Appellee
Dec. 9.	Appearance of counsel for Appellant
1967	
Jan. 17.	Stipulation: Appellant's brief to 2/1/67; Appellee's brief and joint appendix to 3/1/67 (Approved)
Feb. 9.	Stipulation: Appellant's brief to 3/1/67; Appellee's brief and joint appendix to 4/1/67 (Approved)
Apr. 3.	Stipulation: Appellant's brief to 4/15/67; Appellee's brief and joint appendix to 5/15/67 (Approved)
May 18.	Stipulation: Appellant's brief to 6/15/67; Appellee's brief and joint appendix to 7/15/67 (Approved)
Aug. 25.	Stipulation: Appellant's brief and joint appendix to 9/11/67; Appelle's brief to 10/31/67 (Approved)
Sep. 11.	Twenty copies of Brief for Appellant
Sep. 11.	Twenty copies Joint Appendix
Sep. 11.	Proof of service of brief for Appellant and joint appendix
Oct. 30.	Twenty copies of Brief for Appellee
Nov. 22.	Stipulation: Appellant's reply brief to 12/15/67 (Approved)
Dec. 15.	Twenty copies of Appellant's Reply Brief
Dec. 15.	Proof of service of Appellant's reply brief

DATE	PROCEEDINGS
1968	
Jan. 5.	Twenty copies of Appellee's Reply Brief
Jan. 5.	Proof of service of Appellee's reply brief
Feb. 12.	Cause argued and submitted (Before: Combs, McAllister and Cecil, JJ.)
Mar. 13.	Three copies of post-argument memorandum of Appellant with copies of Opinion of Second Circuit in A.M.P. v. Gardner [Distributed to the Court]
Mar. 18.	Three copies Appellee's reply to post-argument memorandum [To Court]
Mar. 18.	Proof of service of Appellee's reply to post-argument memorandum
Mar. 29.	Judgment of the District Court affirmed
Mar. 29.	Opinion by Cecil, J. 5 pp.
Apr. 22.	Mandate issued (No costs taxed)
Apr. 22.	Opinion with mandate

Libel of Information

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

Civil No. 22619

UNITED STATES OF AMERICA

vs.

An article of drug consisting of approximately 5 cases of 55 cartons each, each carton containing 50 clear plastic envelopes of an article labeled in part: (case) "C-6010 Code No. 7011 Control No. 455142 Lot No. 16517—Sterilon Corporation—Buffalo 11, N.Y." (carton) "Bacto-Disks 50 Unidisks—" (envelope) "Bacto Unidisk for Antibiotics Sulfonamides A-S # 1 Low Conc. Tetra Streptomycin Aureo Penicillin Chlor S'Diazine Terra Erythro Code 7011" (package insert) "Sensitivity Testing."

LIBEL OF INFORMATION

[Filed May 25, 1962]

To the Honorable Judges of the United States District Court for the Eastern District of Michigan

Now comes the United States of America by Lawrence Gubow, United States Attorney and Milton J. Trumbauer, Jr., Assistant United States Attorney, both for the Eastern District of Michigan, and respectfully show to this Honorable Court as follows:

1. That this libel is filed by the United States of America and prays seizure and condemnation of a certain article, as hereinafter set forth, in accordance with the Federal Food, Drug and Cosmetic Act (21 USC 334);

2. That Sterilon Corporation, 500 Northland Avenue, Buffalo 11, New York shipped in interstate commerce from Buffalo, New York, on or about March 20, 1962, via Intercity Trucking an article of drug consisting of approximately 5 cases of 55 cartons each, each carton containing 50 clear plastic envelopes of an article labeled in part (case) "C-6010 Code No. 7011 Control No. 455142 Lot No. 16517—Sterilon Corporation—Buffalo 11, N.Y."

(carton) "Bacto-Disks 50 Unidisks—" (envelope) "Bacto Unidisk for Antibiotics Sulfonamides A-S # 1 Low Conc. Tetra Streptomycin Aureo Penicillin Chlor S'Diazine Terra Erythro Code 7011" (package insert) "Sensitivity Testing".

3. No analysis has been made. Article is assumed to contain ingredients listed on its label.

4. That the aforesaid article was misbranded when introduced into and while in interstate commerce within the meaning of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. as follows:

352(1) in that article purports to be and is represented as a drug composed in part of penicillin, streptomycin, chloromycin, tetracycline, and aureomycin, and it is not from a batch with respect to which a certificate or release is in effect pursuant to 21 U.S.C. 357(a) and 357 (c) and the article is not exempt from such requirements.

5. That the aforesaid article is in the possession of Difco Laboratories, 920 Henry, Detroit, Michigan, or elsewhere within the jurisdiction of this Honorable Court.

6. That by reason of the foregoing, the aforesaid article is held illegally within the jurisdiction of the Court and is liable to seizure and condemnation pursuant to the provisions of said Act 21, USC 334;

Wherefore, libelant prays that process in due form of law according to the course of the Court in cases of admiralty jurisdiction issue against the aforesaid article; that all persons having any interest therein be cited to appear herein and answer the aforesaid premises; that this Court decree the condemnation of the aforesaid article and grant libelant the costs of this proceeding against the claimant of the aforesaid article; that the aforesaid article be disposed of as this Court may direct pursuant to the provisions of the said Act; and that libelant have such other and further relief as the case may require.

Lawrence Gubow
United States Attorney

s/ Milton J. Trumbauer, Jr.
Assistant U. S. Attorney

[Affidavit of mailing omitted]

IN THE UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

[Title Omitted]

CLAIMANT'S ANSWER

[Filed October 22, 1962]

The answer of Difco Laboratories, Inc., claimant in the above-entitled case, respectfully represents:

1. That claimant admits the allegations contained in paragraphs numbered 1, 2, 3 and 5 of the libel herein filed and the allegation in paragraph 4 that the article herein libeled, reagent disks, is not from a "batch" of such disks with respect to which a certificate or release is in effect pursuant to 21 U.S.C. 357(a) and 357(c).

2. That claimant denies each and every allegation contained in paragraphs 4 and 6 of such libel, except as heretofore stated with respect to paragraph 4.

And for further answer claimant states that it is the owner of the article herein libeled, that said article consists of reagent disks for laboratory use, and that said article is not misbranded within the meaning or in violation of 21 U.S.C. 352(1) or otherwise.

WHEREFORE having fully answered claimant respectfully prays:

1. That an order be entered allowing claimant to obtain representative samples of the libeled article.

2. That the libel herein filed be dismissed.

3. And for such other and further relief as to the Court may seem just and proper.

DIFCO LABORATORIES, INC.

By s/ H. A. Burnett
President

[Jurat omitted]

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

[Title Omitted]

LIBELANT'S WRITTEN INTERROGATORIES

[Filed May 2, 1962]

Comes now the United States of America, Libelant herein, by Lawrence Gubow, United States Attorney for the Eastern District of Michigan, and submits the following Interrogatories pursuant to Rule 33 of the Federal Rules of Civil Procedure:

* * * *

7. Does claimant admit that:

(a) the particular substances impregnated in the individual circular tips or discs on a given Bacto-Unidisk are brought into contact with specially prepared bacteriological cultures, in the course of the use of the article;

(b) subsequent to the procedure mentioned in (a) above, an observation is made as to whether the substances, or any of them, impregnated in the circular tips appear to have an inhibiting effect upon the growth of the cultures utilized;

(c) as a result of the observation described in (b) above, a chemotherapeutic agent, corresponding to that contained on one of the individual tips or discs of the Bacto-Unidisk, is prescribed for administering to the patient from whom the cultures mentioned in (a) above are taken;

(d) the observation mentioned in (b) above is used to pinpoint the identity of a certain strain of bacteria, which is utilized in the culture, because of the fact that the growth of that certain strain of suspected—but not pre-

cisely identified—organism will be inhibited by a given chemical agent with which one of the individual tips or discs may be impregnated;

(e) some hospitals use antibiotic sensitivity discs to test the resistance of strains of bacteria to the substances with which the antibiotic sensitivity discs are impregnated, which bacterial specimens are taken from doctors, nurses and others in the employ of these institutions;

(f) as a result of the tests described in (e) above, certain employees may be removed from particular hospital wards, such as the maternity or pediatric wards;

(g) the Bacto-Unidisk is intended to provide the physician with the identity and concentration of the antibiotic or sulfonamide to be used in the treatment of the patient from whom the cultures mentioned in (a) above are taken.

* * * *

9. Does claimant admit that the individual tips or discs on the Bacto-Unidisk consist of known amounts of therapeutic drugs such as antibiotics and sulfonamides?

* * * *

11. Is the inhibiting or destructive effect of the drug with which a particular tip or disc of the Bacto-Unidisk is impregnated supposed to show the effects upon the micro-organism in the patient if that drug were administered to the patient?

* * * *

13. Does claimant admit that:

(a) the Bacto-Unidisk is intended to be used to select the drug effective against the chronic or persistent infections present in the patients;

(b) the Bacto-Unidisk is intended to be used and is, in fact, used to select the appropriate antibiotic or sulfonamide to be used in treating patients.

* * * *

16. State fully and in complete detail:

(a) each and every purpose for which antibiotic sensitivity discs are intended to be used;

(b) complete citations to the medical and scientific literature where each use enumerated in (a) above is reported;

(c) the name, address and professional qualifications of each person who formulated or participated in the formulation of each such intended use;

(d) complete citations to the medical and scientific literature which supports, contradicts or varies, or in any manner specifically deals with each such intended use.

17. State fully and in complete detail:

(a) each and every purpose for which Bacto-Unidisks are intended to be used;

(b) complete citations to the medical and scientific literature where each use enumerated in (a) above is reported;

(c) the name, address and professional qualifications of each person who formulated or participated in the formulation of each such intended use;

(d) complete citations to the medical and scientific literature which supports, contradicts or varies, or in any manner specifically deals with each such intended use.

18. State fully and in complete detail:

(a) each and every purpose for which antibiotic sensitivity discs are used;

(b) complete citations to the medical and scientific literature where each use enumerated in (a) above is reported;

(c) the name, address and professional qualifications of each person who formulated or participated in the formulation of each such use;

(d) complete citations to the medical and scientific literature which supports, contradicts or varies, or in any manner specifically deals with each such use.

19. State fully and in complete detail:

(a) each and every purpose for which Bacto-Unidisks are used;
(b) complete citations to the medical and scientific literature where each such use is reported;
(c) the name, address, and professional qualifications of each person who formulated or participated in the formulation of each such use;
(d) complete citations to the medical and scientific literature which supports, contradicts or varies, or in any manner specifically deals with each such use.

20. Outline fully and in complete detail the procedures followed in running antibiotic sensitivity or susceptibility tests with the Bacto-Unidisk.

* * * *

27. Did claimant ever seek direct judicial review, by a Circuit Court of Appeals of the antibiotic sensitivity disc regulations, as finally enacted? If so, provide full details of said review, stating the date of filing and the number and style of the appeal petition, the Circuit Court of Appeals before which the matter was brought, date of hearing or argument, and the final disposition thereof.

* * * *

Lawrence Gubow
United States Attorney

s/ Milton J. Trumbauer, Jr.
Assistant United States Attorney

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

[Title Omitted]

ANSWERS TO LIBELLANT'S WRITTEN INTERROGATORIES

[Filed June 10, 1963]

Difco Laboratories Incorporated, claimant herein, through its President, Harry A. Burnett, submits the following answers to the interrogatories filed on May 2, 1963 by Lawrence Gubow, United States Attorney for the Eastern District of Michigan, on behalf of the United States. The numbers of the answers correspond to the numbers of the interrogatories.

* * * *

7. (a) Yes.
(b) Yes.
(c) Sensitivity disks are used, not only as an indication of relative susceptibility or resistance of organisms isolated from man, but as an indication of susceptibility or resistance of organisms isolated from other environments, e.g., infected plants, infected fish and birds, as well as from other animals or fowl and their products, which may or may not have been treated with antibiotics such as oxytetracycline or chlortetracycline. *Problems of Antibiotics in Foods*, Henry Welch, Jour. AMA, Vol. 170, # 17, Aug. 22, 1959; *A Method for the Rapid Differentiation of Certain Non-Pathogenic Asporogenous Bacilli*, Shewan & Hodgkiss, Nature, Vol. 173:200-209 (1954).

Following the observation described in Interrogatory 7(b), the physician may or may not decide to administer to the patient from whom the cultures mentioned in (a) above are taken, a chemotherapeutic agent corresponding to a substance contained on the disk. The physician's decision will depend upon whether (1) one or more of the substances on the disk appear to exert an inhibiting effect upon the culture; (2) the physician is of the opinion that such substance may be safely and effectively administered

to the patient, taking into consideration known hypersentivity of the patient to the substance causing the inhibition, and (3) the physician concludes, on the basis of his observation and experience, that some other substance may more appropriately be administered. Many factors may enter into the determination of the medication to be administered to a patient. The result of the sensitivity test is one of these factors. *Antimicrobial Therapy in Medical Practice*, Flippin & Eisenberg, F.A. Davis Co., Phila., Pa. (1955); *Testing for Antibiotic Sensitivity in a General Hospital*, Weil & Harris, Annals of Internal Medicine, Vol. 38:1027-1034 (1953).

Where a human patient is involved, treatment of acute infections is ordinarily instituted promptly by the physician without the delay (usually about 24 hours) required to conduct the sensitivity test and the delay which is sometimes required to isolate an organism from the patient (some 24 hours) before the test is undertaken. *The Use and Abuse of Antibiotics in Surgical Patients*, Altemeier & Urelsin, Journal of Michigan State Medical Society, Vol. 61:851-858 (1962); *The Determination of Bacterial Resistance, and its Clinical Significance in Infections of the Urinary Tract*, Moller & Wenckert, Acta Chirurgica Scandinavica, Vol. 101:397-410 (1951); *An Attempt to Integrate the Reliability of Sensitivity Testing with Clinical Response*, Lind, Antimicrobial Agents Annual, p. 478 (1960); *A Guide to Antibiotic Therapy*, Welch, Medical Encyclopedia, Inc., New York, N.Y. (Introduction, p. 3) (1959).

(d) No. Bacto-Unidisks are not intended to and do not "pinpoint the identity of a certain strain of bacteria." The commonly accepted purpose of bringing the impregnated disk into contact with the culture is correctly stated in interrogatory 7(b). The sensitivity test can indicate only the relative susceptibility of the organism in the culture to the chemical substances in the disk. Following a demonstration of susceptibility *in vitro* it can be said only that under the particular test conditions the organism is resistant, moderately resistant, or susceptible to the substance in question. The identity of the organism

can properly be determined only by a study of its morphological, biochemical, serological, and physiological characteristics. *Microbiology*, Pelczar, M.J. & Reid, R.D., McGraw-Hill Book Co., New York, N.Y. (1958); *Bergey's Manual of Determinative Bacteriology*, Williams & Wilkins, 6th Ed., 1948.

(e) Yes. Some hospitals make use of sensitivity disks to determine the relative susceptibility of organisms isolated from hospital personnel. Some hospitals also make use of these laboratory tools as an indication of the resistance to subtances contained on the disk of organisms isolated from inanimate objects such as tables, nursing bottles, window ledges, floors, bedpans, fomites. *Antibiotic Therapy for Staphylococcal Diseases*, Welch & Finland, Medical Encyclopedia, Inc., New York, N.Y. (1959); *Staphylococcal Infections in the Hospital and Community. Hospital Environment and Staphylococcal Disease*, Ravenholt, R.T. and Ravenholt, O.H., Am. J. Publ. Health, Vol. 48 (March 1958); *Control of Staphylococcal Infection in Hospitals*, Starkey, The Canadian Medical Association Journal, Vol. 75:371, (1956).

(f) Yes. It is claimant's understanding that such action has occurred, but we have no actual knowledge of whether removal of employees has been based in part on the results of sensitivity tests with Bacto-Unidisks.

(g) No. Bacto-Unidisks are intended to provide an indication of whether a given culture is susceptible to one or more of the kinds of substances on the Unidisk. Tests with Bacto-Unidisks are not intended to nor do they inform the physician of the *concentration* of the inhibiting antibiotic or sulfonamide which should be administered to the patient from whom the test culture has been isolated, assuming the physician uses a chemotherapeutic agent corresponding to a substance on the disk. Susceptibility of the organism is indicated by a zone of inhibition of its growth around the sensitivity disk. The *width* of the zone is a measure of the diffusibility of the antibiotic or sulfonamide in agar. It is not a measure of the appropriate concentration to be used in treatment of the patient or of potential antibacterial activity of a chemo-

therapeutic agent. The use of sensitivity disks is strictly a laboratory testing device. *Antibiotic Sensitivity Testing* (an editorial), Welch, Antibiotic Medicine, Vol. 2, #5, (May, 1956); *The Rationale of Routine Antibiotic Sensitivity Determinations*, Lind, Antibiotics & Chemotherapy, Vol. 3:672-676 (1953).

When the identity of a chemotherapeutic agent active against an infecting organism is known or suspected, the physician decides upon the treatment to be used. In so doing he will be guided by his clinical judgment and his knowledge of the agent under consideration; its diffusibility in tissue (if it is to be injected); its absorption from the gut (if given by mouth); its toxicity; the patient's weight, age, allergic state and degree of illness, and other considerations pertinent in the medical situation presented. None of the kinds of substances contained on the disk may be found suitable for treatment. Furthermore, treatment ordinarily will not have been delayed awaiting organism isolation or the sensitivity test. In that event, the decision of the physician will be whether to continue or discontinue a treatment already underway, based upon factors such as those above mentioned. *Principles & Practice of Antibiotic Therapy*, Henry Welch in Collaboration with Braley, Clark, Dowling, Finland, Herrell, Hinshaw, Hobby, Keefer, Knight, Pulaski, Rein, Ross, Smadel, Weinstein, Woodward, and Zander, Medical Encyclopedia, Inc., New York City (1954).

* * * *

9. Claimant admits that Bacto-Unidisks contain known amounts of chemical substances corresponding to substances which are used as drugs. Claimant denies the disks or the antibiotic substances or the sulfadiazine on the disks are drugs within the meaning of the Federal Food, Drug and Cosmetic Act. In the physical state and quantities in which they are present on the disks these substances are not available as therapeutic agents nor are such substances or the disks containing them intended for therapeutic or drug use.

* * * *

12. As stated in previous answers, the inhibition of growth of a micro-organism by an antibiotic or sulfonamide following proper laboratory use of a Bacto-Unidisk is an indication of the effect the corresponding drug might have if brought into contact with the same microorganism through administration to an infected patient. It is well known, however, that this is not always the case. An antibiotic, for example, may show excellent inhibition in an *in vitro* laboratory test, yet fail to give the desired therapeutic result *in vivo*, because of numerous factors brought into play when a substance is introduced into the body, which are not present in the laboratory test. *Guide to Antibiotic Therapy*, Henry Welch, Medical Encyclopedia, Inc., New York City, Introduction, p. 3 (1959); *Antibiotic Sensitivity Testing by the Disk Method*, Anderson, T. G. and Troyanovsky, A., Antibiotics Annual, 587-595 (1959-60); *The Value of Bacterial Sensitivity Testing in the Treatment of Urinary Tract Infections* (a Study in Correlations), Swanton & Lind, Antibiotics Annual (1956-57) 191-195, Medical Encyclopedia, Inc., New York, N.Y. (1957); *Comparison Between Clinical Results and Bacterial Sensitivity Test in the Treatment of Urinary Tract Infections with Chemotherapy*, Giertz and Gullbring; Acta Chirurgica Scandinavica, Vol. 102: 121-127 (1951); *Comparison of Methods for Determining Sensitivity of Bacteria to Antibiotics in Vitro*, Jackson & Finland, A.M.A. Archives of Internal Medicine, Vol. 88: 446-460 (1951); *In Vitro Sensitivity of Coliform Bacilli to Seven Antibiotics*, Frank, Wilcox and Finland, J. Lab. & Clin. Med. Vol. 35:188-204 (1950).

* * * *

13. (a) and (b). As stated in preceding answers, claimant admits that Bacto-Unidisks are intended to be used as laboratory tools to aid the physician in determining whether one or more of the antibiotics or the sulfonamide (or both) contained in the disk are active against microorganisms, including those isolated from patients with chronic or persistent infections. Moreover, with the presently available antibiotics and sulfonamides more than one may frequently be shown to be apparently ap-

plicable in a given case based on sensitivity tests or other criteria. In such cases obviously the physicians "drug of choice" is determined by factors beyond the laboratory procedure such as comparative toxicity of the antibiotics and/or sulfonamides, their mode of administration, the blood concentrations attainable, their rate of excretion, the nature of the disease, involvement of the patient in other noninfectious, debilitating diseases, and the allergic history of the patient.

As heretofore indicated, the physician "selects" the antibiotic and/or sulfonamide based on his clinical judgment and all of the known facts; the sensitivity test, with Bacto-Unidisks, acts as a laboratory tool presenting a part of the overall picture.

It must be kept in mind that the isolation of the infecting organism and the tests for its degree of sensitivity to these substances is time consuming and as indicated earlier frequently treatment has already been instituted before these laboratory procedures can be completed.

An antibiotic may show marked inhibition with a sensitivity test yet fail to give the desired therapeutic result, e.g., penicillin in certain chronic staphylococcal infections. *Antibiotic Therapy of Staphylococcal Diseases*, Welch and Finland, Antibiotics Monographs # 12, Medical Encyclopedia, Inc., New York City (1959); *A Guide to Antibiotic Therapy*, Henry Welch, Medical Encyclopedia, Inc., New York City (1959); *Rational Use of Antibiotics in Hospitals*, Hans Ericsson, The Scandinavian Journal of Clinical and Laboratory Investigation, Vol. 12: 34-35, Supplement 50 (1960); *Antibiotic Therapy: Correlation of Clinical Results with Laboratory Sensitivity Tests*, Roger and Branch et al., The Canadian Medical Association Journal, Vol. 74: 605-612 (1956).

* * * *

16, 17, 18, 19. There are three methods in more or less general use in the determination of antibiotic sensitivity: the broth serial dilution, the agar plate dilution, and the agar diffusion techniques. The most widely employed, because of its simplicity, is the latter—the diffusion meth-

od—using sensitivity disks. These disks may be prepared in the laboratory or purchased commercially.

One of the uses and intended uses of sensitivity disks is in laboratory techniques involving a determination of the susceptibility of cultures of microorganisms to the action of antibiotics. This applies to Bacto-Unidisks.

The Scientific literature is replete with references to the uses of laboratory sensitivity tests and their uses as an aid in determining susceptibility of microorganisms. To list all pertinent references, which would include the related literature on the substances (including antibiotics) used in the tests, would require an inordinate amount of time and a survey covering a period of many years. The references herein given appear adequate to establish the proper answers to the interrogatories.

The claimant therefore asserts that Bacto-Unidisks are "intended for" and "used" as an aid in determining the susceptibility of microorganisms generally in the same manner as all other sensitivity disks, e.g., such tests may be carried out in hospitals as aid in determining the incidence of resistant staphylococci among hospital personnel, in determining resistance of organisms isolated from patients or from inanimate objects such as floors, window ledges, bedpans, fomites, etc. in hospitals; in determining the presence of resistant organisms in chronic wounds; in demonstrating the presence or activity of penicillinase in bacterial cultures.

Antibiotics are used, not only in the prophylaxis and treatment of human diseases, but in other fields. For example, antibiotics are used in animal nutrition for the promotion of the growth of swine, chicks and poults. In agricultural research laboratories and others sensitivity tests have been used on cultures isolated from animals so treated as an aid in determining emergence of resistant microorganisms.

Large quantities of antibiotics are used therapeutically and prophylactically in animals such as cows, beef cattle, swine, chicks, and mink. As an aid in determining the emergence of resistant strains following such use sensitivity tests are performed in a variety of research laboratories on cultures isolated from such animals.

The use of antibiotics as crop sprays to prevent blight in apples, pears, walnuts, and beans and bacterial diseases of tobacco, tomatoes, peppers and cherries has prompted the use of sensitivity tests as an aid in determining the emergence of resistant microorganisms after such sprays are used.

In all of the above procedures, Bacto-Unidisks or similar especially prepared disks made in the research laboratory may be used. Their functions are the same, i.e., an aid in determining the susceptibility of a given organism to an antibiotic substance regardless of the source of the culture under test. *Antibiotics in Food Preservation*, Henry Welch, Public Health and Regulatory Aspects, Science, Vol. 126, No. 3284 (Dec. 6, 1957), Jour. Applied Nutrition, Vol. 11: 133-38 (1958); *Problems of Antibiotics in Food as the Food and Drug Administration Sees Them*, Henry Welch, Am. Jour. Publ. Health, Vol. 47, No. 6 (June, 1957), *Chemotherapy In Infections Diseases*, Henry Welch, American Professional Pharmacist (Nov. 1954).

20. Susceptibility Tests Using Bacto-Unidisks: Prepare Petri plates with Bacto-Heart Infusion Agar, Bacto Tryptose Blood Agar Base or Bacto-Mueller Hinton Medium each with or without five per cent sterile defibrinated rabbit, horse, sheep or beef blood. Use 20 ml. of final medium per 95 mm. petri dish bottom.

Inoculate the surface of the medium with the specimen or culture to be tested by smearing or streaking in a manner to give confluent growth. A lighter inoculum is recommended for testing susceptibility to sulfonamides than for antibiotics. One drop (0.05 ml.) of a 1:100 dilution of an 18-hour culture in Bacto-Brain Heart Infusion per plate is adequate. Also, Mueller Hinton Medium free from sulfonamide inhibitors is recommended for sulfonamide sensitivity testing.

Aseptically remove a unidisk from its package using a sterile forceps and place it on the inoculated medium surface. Make sure the ring and integral parts of the unidisk are all in intimate contact with the medium to permit maximum diffusion of the antibiotics and sulfonamide.

Incubate the inoculated plates on which the unidisk is placed at 35-37° C. for 18-24 hours. Remove plates from the incubator and observe for zones of inhibition around the tips of the unidisk.

The results obtained with Bacto-Unidisks as with other sensitivity tests similarly conducted, are of a qualitative rather than a quantitative nature. The many variables that enter into a test of this type, such as the size of the inoculum, type of growth of the organism, amount of inoculum on the plate, thickness of the medium, incubation conditions, rate of diffusion and the rate of deterioration of the chemotherapeutic agent during incubation, preclude a precise quantitative nature. Sensitivities are to be determined by the presence and not by the size of the zone of inhibition around the disk.

Sensitivity to an antibiotic or sulfonamide available in one concentration only should be reported as "sensitive" or "resistant."

The sulfonamide sensitivity test should be read as soon as growth develops and zones of inhibition are discernible. Many organisms produce sulfonamide inhibitors which upon prolonged incubation diffuse into the zones of inhibition neutralizing the inhibitive effect of the sulfonamide and give an erroneous result. Double zones of growth result from this cause.

* * * *

27. No.

* * * *

s/ H. A. Burnett

[SEAL]

[Jurat omitted]

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

[Title Omitted]

CLAIMANT'S REQUESTS FOR ADMISSIONS

[Filed June 25, 1968]

Claimant, Difco Laboratories Incorporated, requests libelant, United States of America, within 20 days after service of this request to make the following admissions for the purpose of this action only and subject to all pertinent objections to admissibility which may be interposed at the trial:

That each of the following statements is true:

1. That Bacto-Unidisks, the article under seizure, are labeled "for laboratory use."

2. (a) That many chemicals which are drugs when intended for drug use are not regarded as drugs by the Food and Drug Administration (FDA) when intended for non-drug use.

(b) That one of the factors pertinent in determining whether a chemical is intended for drug use is its labeling.

3. That reagents labeled for laboratory use have not, as a general class, been treated as drugs by FDA.

4. That Bacto-Unidisks are used in laboratory procedures to determine whether, under test conditions, one or more of the chemical components of the disks are active against particular microorganisms.

* * * *

12. (a) That FDA has issued no regulation providing for the certification of sensitivity disks containing a combination of antibiotics and sulfadiazine and that such disks will not be certified by FDA unless such a regulation is issued and becomes effective.

(b) That Part 147 of the FDA antibiotics regulations (21 CFR Part 147) entitled "Antibiotics Intended for Use in the Laboratory Diagnosis of Disease" which provides for tests and methods of assay, and certification procedure for "sensitivity disks" does not include the Bacto-Unidisks under seizure herein, which contain sulfadiazine.

13. That the proceedings which led to the present regulations providing for certification of certain antibiotic sensitivity disks therein described, entitled "Antibiotics Intended for Use in the Laboratory Diagnosis of Disease" (21 CFR Part 147) were instituted upon the initiative of the Commissioner of Food and Drugs by a "Notice of Proposed Rule Making" published in the Federal Register of April 9, 1960.

14. That sensitivity disks containing only a substance or substances which are not antibiotics, are not considered certifiable by FDA.

* * * *

16. That certain antibiotic substances, including some components of Bacto-Unidisks, are used as growth stimulators for plants, for the prevention and treatment of plant diseases, to disinfect soils, and to treat seeds, or for one or more such agricultural purposes, and when intended solely for any such use are not considered by FDA as drugs.

17. That antibiotic substances which are in fact used and are intended solely for the agricultural uses described in request No. 16, *supra*, are not considered certifiable by FDA, regardless of whether they contain suitable denaturants that make them unfit for drug use.

18. (a) That certain antibiotic substances, including some components of Bacto-Unidisks, are used in laboratories for the purification of microbial cultures and the purification of bacteriophage.

(b) That when intended solely for the purification of microbial cultures or bacteriophage and when so used, antibiotics are not treated as drugs in FDA regulations.

19. That antibiotic substances are not considered cer-

tifiable by FDA unless they are intended for drug use or are "recognized" in an official compendium.

20. That no form of sensitivity disk (including Bacto-Unidisks) is listed in any of the three "official compendia" (the United States Pharmacopoeia XVI, the National Formulary XI, or the Homeopathic Pharmacopoeia of the United States.)

21. That prior to the promulgation of 21 CFR 146.53, published in the Federal Register of June 16, 1949, which was later redesignated as 21 CFR 146.24, FDA had not issued a regulation exempting sensitivity disks from certification or requiring certification of such disks.

22. That the following administrative orders promulgating regulations providing for certification of antibiotic drugs and tests and methods of assay for such drugs (a) were not preceded by publication in the Federal Register of notice of proposed rule making, and (b) were published in final form and as so published did not provide an opportunity for interested persons to file objections thereto and to request a public hearing thereon:

(i) The order published in the Federal Register of September 1, 1945 (10 FR 11227), providing for certification of penicillin-containing drugs (21 CFR Part 146).

(ii) The order published in the Federal Register of September 8, 1945 (10 FR 11478), providing tests and methods of assay for penicillin (21 CFR Part 141).

(iii) The order published in the Federal Register of April 4, 1947 (12 FR 2231), providing new regulations for certification of penicillin-containing drugs and streptomycin-containing drugs.

(iv) The order published in the Federal Register of April 4, 1947 (12 FR 2215) amending 21 CFR Part 141 to provide tests and methods of assay for streptomycin.

(v) The order published in the Federal Register of August 13, 1949 (14 FR 5006) amending 21 CFR Parts 141 and 146 to provide for certification and

tests and methods of assay for aureomycin, chloramphenicol, and bacitracin.

(vi) The order published in the Federal Register of June 16, 1949, promulgating Section 146.53 of the FDA antibiotic regulations (21 CFR 146.53) later redesignated as 21 CFR 146.24, exempting from certification certain "antibiotics for diagnostic use."

23. That the Secretary of Health, Education, and Welfare or his predecessor the Federal Security Administrator, or the Commissioner of Food and Drugs, pursuant to authority delegated to him, has from time to time, promulgated and caused to be published in the Federal Register, orders other than those designated in Request No. 22, *supra*, providing for regulations under Section 507 of the Federal Food, Drug and Cosmetic Act (21 USC 357) which (a) were not preceded by publication in the Federal Register of Notice of proposed rule making, and (b) were final orders which offered no opportunity to interested parties to object to such orders or to request a hearing thereon; and that one or more of such orders have been published subsequent to the promulgation of the final order adding part 147 to Volume 21 of the Code of Federal Regulations (relating to certification, tests, and assays of antibiotic sensitivity disks), which was published in the Federal Register of September 30, 1960 (25 FR 9369).

24. (a) That, upon enactment of the Drug Amendments of 1962 (Public Law 87-781, 76 Stat. 780) the Department of Health, Education & Welfare under date of October 10, 1962, released a document entitled "Drug Amendments of 1962, Federal Food, Drug & Cosmetic Act—Summary," in connection with a statement by Secretary Anthony J. Celebrezze concerning the amendments, and that the "Summary" states, under the heading "Batch Certification of Antibiotics"—

"14. All antibiotic drugs *to be administered to humans* are made subject to batch-by-batch testing and certification by FDA for identity, strength, quality and purity to assure that they are safe and effec-

tive before they are released for sale." (Emphasis supplied.)

(b) That the Department of Health, Education and Welfare issued a printed pamphlet, dated November 1962, entitled "Summary of the Drug Amendments of 1962," and that such pamphlet contains, on page 8, under the heading "Batch Certification of Antibiotics," the statement quoted under (a) above.

25. (a) That claimant, by letter of May 6, 1960, signed on its behalf by H. C. Nelson, filed with the Department of Health, Education and Welfare, comments on a "Notice of Proposed Rule Making" published in the Federal Register of April 9, 1960, proposing regulations for tests and methods of assay and certification of sensitivity disks.

(b) That, in the letter referred to in (a) above claimant objected to the proposed regulations on the grounds, among others, that sensitivity disks are not certifiable antibiotic drugs.

(c) That claimant, by letters of October 19, October 27, and October 28, 1960, signed by H. C. Nelson filed objections on the grounds stated in (b) above, to the order establishing regulations for tests and methods of assay and certification of sensitivity disks published in the Federal Register of September 30, 1960 and requested a public hearing on such objections.

* * * * *

s/ Corliss, Lette & Moody

by Alexander P. Lette
Corliss, Lette & Moody
Alexander P. Lette
1424 Ford Building
Detroit 26, Michigan

s/ Edward Brown Williams
Edward Brown Williams
411 Washington Bldg.
Washington 5, D. C.

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

[Title Omitted]

ANSWERS TO CLAIMANTS REQUESTS FOR ADMISSIONS

[Filed July 25, 1963]

The United States of America, Libelant herein, submits the following answers to Claimant's Requests for Admissions.

1. Yes.
2. (a) Yes.
   (b) Yes.
3. Yes.
4. No. While it is true that the Bacto-Unidisk may be used for such purpose, the Bacto-Unidisk involved in this action was intended for use in the diagnosis, cure, mitigation, and treatment of disease.

* * * * *

12. (a) Yes. However, under 21 C.F.R. 146.7 the Secretary may certify sensitivity discs containing a combination of antibiotics and other chemotherapeutic agents, such as sulfadiazine, upon request and submission of the required data by the person or firm making such request.
   (b) Yes.
13. Yes.
14. Yes. But see Admission No. 12(a), *supra*.

* * *

16. Yes. But it should be pointed out that components of Bacto-Unidisks, as such are never used for the purpose set forth in request No. 16; antibiotics substances, similar to those with which the Bacto-Unidisks are impregnated, may be used for such purposes.
17. Yes. However, this seizure action concerns itself with Bacto-Unidisks, which are intended for use as drugs within the meaning of 21 U.S.C. 321(g).

18. (a) Yes.
(b) Yes.
19. Yes. But see 21 U.S.C. 321(g).
20. Yes.
21. Yes.
22. (i) to (vi): Yes. However, these regulations referred to in Request No. 22 were enacted in full compliance with the statutes in effect at that time.
23. Yes.
24. (a) Yes. However, the clear purpose of this statement was to indicate that veterinary antibiotics were not intended to be covered by the new antibiotic amendments.
(b) Yes. See 24(a).
25. (a) Yes.
(b) Yes.
(c) No. Libelant has the letter of October 28, 1960, referred to in this request, but has no record of the letters of October 19, 1960, or October 27, 1960. However, Libelant does have, in its files, letter dated December 19, 1960.

* * * *

s/ Gilbert S. Goldhammer
Gilbert S. Goldhammer

[Jurat Omitted]

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

[Title Omitted]

CLAIMANT'S AMENDED ANSWER

[Filed December 11, 1963]

By leave of Court, Difco Laboratories, Inc., claimant in the above entitled case, hereby amends its answer heretofore filed herein and respectfully represents:

1. That claimant admits the allegations contained in paragraph 1 of the libel filed herein.

2. That claimant denies the allegation contained in paragraph 2 of such libel that Bacto-Unidisks, the article shipped as therein alleged, is an article of drug, and admits the remaining allegations of paragraph 2.

3. That claimant admits the allegations of paragraph 3 of such libel.

4. (a) That claimant denies the allegations of paragraph 4 of such libel that such article is misbranded as alleged and that such article purports to be and is represented as a drug;

(b) That claimant admits the allegations of paragraph 4 of such libel that such article is composed in part of penicillin, streptomycin, chloromycetin, tetracycline, and aureomycin; and claimant admits that such article is not from a batch with respect to which a certificate or release is in effect pursuant to 21 U.S.C. 357(a), and that such article has not been exempted by regulations issued pursuant to 21 U.S.C. 357(c) or (d).

5. That claimant admits the allegations of paragraph 5 of such libel.

6. That claimant denies each and every allegation contained in paragraph 6 of such libel.

And for further answer claimant states that it is the owner of the article herein libeled, that said article consists of reagent disks for laboratory use, and that said

article is not misbranded within the meaning or in violation of 21 U.S.C. 352(1) or otherwise.

WHEREFORE having fully answered claimant respectfully prays:

1. That an order be entered allowing claimant to obtain representative samples of the libeled article.
2. That the libel herein filed be dismissed.
3. And for such other and further relief as to the Court may seem just and proper.

DIFCO LABORATORIES, INC.

By s/ H. A. Burnett
President

[Jurat Omitted]

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

Civil Action No. 22619

UNITED STATES OF AMERICA

v.

ARTICLE OF DRUG * * * BACTO UNIDISK * * *

ORDER DENYING MOTION FOR SUMMARY JUDGMENT

[Filed April 6, 1965]

Libelant has moved for summary judgment. Oral argument was had in open court, briefs submitted to the Court, and both pre- and post-hearing affidavits filed. The affidavits are those of doctors and have been filed by each

party to this condemnation proceeding. In this suit the government has libeled an article referred to as "Bacto Unidisk" claiming that the article is misbranded within the meaning of 21 U.S.C. 352(1) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 334) in that it "purports to be and is represented as a drug composed in part of penicillin, streptomycin, chloromycin, tectracycline, and aureomycin, and it is not from a batch with respect to which a certificate or release is in effect pursuant to 21 U.S.C. 357(a) and 357(c) and the article is not exempt from such requirements."

Claimant, Difco Laboratories, contends in its amended answer that the article is not a drug and is not misbranded. The article in question is described by claimant in its brief in opposition to libelant's motion for summary judgment as follows:

> "Bacto-Unidisks, the brand name of the product, under seizure, referred to generically as 'sensitivity disks,' are reagents used for laboratory testing of the sensitivity of microorganisms to chemicals with which the disks have been impregnated. Sensitivity disks manufactured by claimant may be single units bearing a single chemical or they may be composed of several units extending inward from a ring (somewhat like truncated spokes of a wheel), each bearing a separate chemical. Bacto-Unidisks are of the second type with eight paper units extending inward from a paper ring, each of seven of which is impregnated with a different chemical commonly used as an antibiotic drug and an eighth with a chemical—sulfadiazine—which is also commonly used as a drug but which is not an antibiotic."

The government has cited to the Court the case of *U. S. v. Consolidated Laboratories, Inc.*, Civil No. 63-C-23, N.D. Ill., March 29, 1963, in support of its position that the article in question is, in fact, a drug. The court there decided the case before it upon stipulation by counsel "that the trial of this matter shall be had on the evidence and exhibits adduced at the hearing on the motion of the

United States for a preliminary injunction." This situation does not prevail here. This is the government's motion for summary judgment. The parties have not stipulated that the case be decided on the basis of the pleadings and affidavits on file and the oral argument on the motion. On the contrary, the claimant in this action contends that there are genuine issues as to material facts that preclude summary judgment procedure. Inasmuch as the affidavits filed herein by the various doctors consist of statements and opinions that are susceptible of varying interpretations, it is the Court's view that some or all of such affiants should be produced in court so that there may be expansion and elucidation of the matters contained in the affidavits.

A trial of the issues here involved appears at this posture of the case to be indicated. Perhaps it will be possible to utilize procedure for streamlining the trial proceedings. This matter may be taken up at the pre-trial conference.

It is Hereby Ordered that the motion for summary judgment be and the same is hereby denied.

s/ Thomas P. Thornton
Thomas P. Thornton
United States District Judge

April 6, 1965.

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

[Title Omitted]

TRANSCRIPT OF TESTIMONY

Proceedings had in the above-entitled matter before Honorable Thomas P. Thornton, District Judge, at Detroit, Michigan, commencing on Tuesday, May 18, 1965, at nine-thirty o'clock in the forenoon.

APPEARANCES:

MILTON J. TRUMBAUER, JR., Esq.,
SALVATORE L. FRANCHINO, Esq.,

Appearing on behalf of the Libelant.

EDWARD BROWN WILLIAMS, Esq.,
JOHN K. WORLEY, Esq.,

Appearing on behalf of the Claimant.

* * * *

[8] Mr. Trumbauer: * * * The point I want to emphasize to the Court at this point is that the thrust of the Government's case [9] will be that definition of a drug which is encompassed and specified under Title 21, Section 321 (g) (2), namely:

(Reading):

"* * * articles intended for use in the diagnoses, cure, mitigation, treatment, or prevent of disease in man or other animals."

The Court: Well, are you relying upon any part of that diagnosis or—

Mr. Trumbauer (interposing): We intend to show from testimony, we intend to prove from testimony that this article, the subject of this lawsuit, is, in fact, an article which is intended for use—I would say that the

proofs will show—primarily in the area in the use in treatment of disease.

The Court: Treatment.

Mr. Trumbauer: Also, to some extent, in the diagnosis of disease. And, in a larger sense, even in the prevention of disease.

But primarily the key areas of the definition under (g) (2) would be in treatment and its corresponding conclusion, that is when you are trying to treat something you are trying to cure it.

Both of those words are used in the definition "treatment" and "cure" of disease.

[10] The Court: . Well, you are not principally relying upon diagnosis, then?

Mr. Trumbauer: Not as strongly, your Honor, as we intend to show it would be used in the treatment.

But the diagnosis area will also be, we believe, shown to be an area that this article can be used for.

Essentially, then, that it is the type of drug, once having brought it within that concept of "drug," that it is an antibiotic drug, and, because it is an antibiotic drug, that Congress has seen fit under Section 352(1)—

The Court (interposing): What is that section?

Mr. Trumbauer: 352(1).

The Court: All right.

Mr. Trumbauer: To-wit, that if an article

(Reading):

> "is, or purports to be, or is represented as a drug composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, or bacitracin, or any derivative thereof."

that these are misbranded unless they are certified, come within the certification provisions and the authority of the Food & Drug Administration to promote regulations for [11] the purpose of certification as set forth under Title 21, Section 357(a) and also 357(c).

* * * *

Mr. Williams:

[13] Furthermore, I might add that in the 1962 [14] Drug Amendments, when the certification system was extended to all antibiotics, it was executed in these specific terms, "To all antibiotics for use by man," and that particular phrase has itself been interpreted by a release of the Department of Health, Education & Welfare to mean for administration to humans.

That is all I have to say on that.

The Court: All right. Call your first witness.

Mr. Trumbauer: Before calling the first witness, your Honor, may we, counsel, stipulate with the Court's permission into the record the written interrogatories which were prepared by the libelant, and the claimant's answers thereto, and the request for admissions prepared by the claimant and the libelant's answers thereto?

Mr. Williams: Yes.

Mr. Trumbauer: They may become part of the record, your Honor.

The Court: As far as I am concerned, if they are in the file, they are part of the record. Anything that is in that file is part of the record.

Mr. Trumbauer: All right.

Mr. Williams: Your Honor, I would like to have one of the scientific people from the Difco Laboratories [15] sitting here during the next proceeding.

The Court: All right.

Mr. Williams: Next part of the proceeding.

The Court: All right.

Mr. Trumbauer: Again before calling the first witness, I would like to have the Reporter mark this as Exhibit No. 1 for identification.

(A box of Bacto-Unidisks was thereupon marked Libelant Exhibit 1 by the Reporter.)

Mr. Trumbauer: I would like to offer into evidence, your Honor, and I believe counsel will so stipulate, that Government's or Libelant's Exhibit No. 1 is a representative sample from the total collection of items that were seized as a result of the filing of the libel information, which is now Civil No. 22619.

In other words, it is one box of the Bacto-Unidisks which are the subject of this lawsuit.

The Court: Any objection?

Mr. Trumbauer: And also contains the insert which normally accompanies the box as part of its label.

The Court: Any objection?

Mr. Williams: No, sir.

The Court: It is admitted, with the contents.

Mr. Trumbauer: The Government calls at this [16] time Dr. Joseph Truant.

DR. JOSEPH PAUL TRUANT was thereupon called as a witness on behalf of the Libelant and, having been first duly sworn, testified as follows:

Direct Examination

By Mr. Trumbauer:

Q. Your full name, witness?

A. Joseph Paul Truant.

Q. And your address, sir?

A. 3617 Bradford Drive, Birmingham, Michigan.

Q. And what is your occupation, sir?

A. I am a medical bacteriologist.

Q. And with what organization are you associated in that capacity?

A. With Henry Ford Hospital here in Detroit.

Q. What is your particular position at the Henry Ford Hospital?

A. I am Chief of the Bacteriology Section in the main laboratory department at the hospital.

Q. Are you, then, what is known as a microbiologist?

A. Yes.

Q. And are you also technically known, then, as a bacteriologist?

A. Yes. Microbiology encompasses the various specialties of microbiology, namely, bacteriology, mycology, parasitology, virology.

[17] Now I am particularly concerned with the mycology and bacteriology phases of microbiology.

Q. Can you give the Court, Dr. Truant, some indication of your education and training in this field?

A. I am a graduate of the University of Toronto.

I received my Bachelor of Science from the University of Toronto; my Master's and Ph.D. from the University of Western Ontario Medical School.

I have spent five years teaching Chemistry and Bacteriology at Assumption University and Holy Name in Windsor, the Windsor area.

I spent three years teaching and being an Associate in Medical Microbiology at the University of Western Ontario Medical School.

I have spent the last ten years being Chief of the Bacteriology Section at Henry Ford Hospital, and have spent some thirteen, the last thirteen years, in clinical microbiology; various aspects of routine diagnostic microbiology; developmental microbiology; and I also head up the research microbiology at the hospital.

Q. And have you prepared any theses or any items for publication in this field?

A. Yes, I have two theses which were concerned with the nuclear structure of microorganisms, and I have published from [18] forty-five to fifty publications, fifteen of these dealing with antibiotic development and research.

Q. Do you belong to any societies, professional societies in this field?

A. Yes. I am a member of the American Society for Microbiology; also a member of the Michigan Branch of the National Society; member of the American Public Health Association; a member of the Canadian Microbiology Society; and I am presently Chairman of the Clinical Section, of the Medical Division, of the American Society of Microbiology.

Mr. Trumbauer: Would you mark this Libelant Exhibit 2.

(A document entitled, "Vita, Joseph Paul Truant," was thereupon marked Libelant Exhibit 2 by the Reporter.)

Q. (By Mr. Trumbauer, continuing): I show you what has been marked as Libelant Exhibit No. 2 for identifica-

tion and ask you to look that over, and ask you if you can identify it? (Handing exhibit to the witness.)

A. This curriculum vita is not up to date. It omits several of the papers published this year.

Q. I see. Other than that, is it an accurate summary of your qualifications from a standpoint of education, associations, and publications in the field of microbiology and bacteriology?

[19] A. Yes, it is.

* * * *

Q. (By Mr. Trumbauer, continuing) Now, in your work as Chief of Bacteriology at Henry Ford, can you give us some idea of just what you do there in terms of the total number of operations that you perform in your particular field?

A. Yes. We are responsible for the majority of specimens which have requests for bacteriological and mycological isolates. We have—

Q. (Interposing) Would you explain what you mean by "mycological isolates"?

A. Mycology includes the study, the isolation of the—especially the pathogenic fungi. It includes the isolation of the saprophytic or the so-called non-pathogenic fungi as well.

So, mycology is the study of the fungi.

[20] Q. In your area of activity do you get into the field of what is known as "susceptibility testing"?

A. Yes. One important function of our laboratory is to perform susceptibility tests on the isolates which are considered to be pathogenic, or, in other words, which are capable of producing disease in the individual.

So, whenever organisms are isolated, in a large majority of cases we do susceptibility tests on these organisms.

Q. And could you give us some idea of how many individual type of susceptibility tests are run under your direction and control in this hospital?

A. Yes. We perform some twelve hundred to fifteen hundred susceptibility tests per month.

Now, a susceptibility test does not merely mean one disk on a plate, but on a plate we have eight individual or nine individual disks, and I am talking about one susceptibility test being a complete test on that particular organism.

We are not counting individual chemotherapeutic disks which are being used, but, rather, the number of organisms that have been tested.

If you wanted a total count of the individual number of individual disks which were used, it would be of the order of [21] ten thousand per month or thereabouts.

Q. Now, in the field of susceptibility testing, are there different methods of testing that are generally utilized?

A. Yes. There are several well-recognized procedures. The most commonly used in diagnostic work throughout this country is the antibiotic agar disk procedure.

The second one, not necessarily in terms of the number of times it is used, is the tube dilution procedure.

Q. Can you just—go ahead. I am sorry. I did not mean to interrupt you.

A. The third method is one where you might incorporate the antibiotic within the media. And there are various modifications of these, where one may impregnate strips with the antibiotic and overlay the organism that is growing on the agar.

So there are several methods.

The ones that are probably most frequently used are the agar disk procedure and the tube dilution procedure.

Q. What is the—briefly, what is the tube dilution procedure?

A. The tube dilution procedure consists of the addition of antibiotic to culture media, fluid media, in required dilution. In other words, you might have one microgram per millilite: of broth, five micrograms, ten micrograms. All of these are [22] "per mls." of media.

And then, having prepared these antibiotic dilutions in broth, one proceeds to add a relatively uniform concentration of an inoculant, be that somewhere in the range of ten to the sixth, to ten to the twelfth microorganisms per ml.

[23] A. The susceptibility test is a determination of the degrees of susceptibility or resistance—of sensitivity or resistance of a particular organism. The organism is usually an isolate from the patient which may be the cause of the patient's disease.

Q. What do you mean, in layman's terms, by "an isolate from the patient"?

A. An isolate is similar to a microorganism bacteria or germ.

The Court: Is it a discharge from a patient or is it an infection that is present in the patient?

A. It is found in a specimen obtained from the patient.

The Court: It may be in sputum or it might be—

A. (Interposing) In sputum, blood, urine, wounds, abscesses. Things of this sort.

Q. (By Mr. Trumbauer, continuing) Yes.

A. In other words, in answering his Honor's question, it is part of the discharge.

The Court: All right.

Q. (By Mr. Trumbauer, continuing) And you take this discharge [24] from the patient, from the human patient, and what do you do with it with respect to this susceptibility testing?

A. We transfer—what we term inoculate this specimen onto culture media, and the culture media permits the organism to grow, and we examine the growth usually after an eighteen-hour period, and the examination is one where we identify what we consider to be the causative organism or germ, either as a single species or single-type, or there may be multiple types of germs.

Q. Now, for example, at the Henry Ford Hospital, from whom do you, as the laboratory supervisor, obtain this specimen?

A. The nurses on the floors are given the orders by the physicians to collect a certain type of specimen. They collect this specimen from the patient, and then they send it on to the laboratory, and we handle it from there on by the procedure that I have just outlined.

Q. And once it gets into your hands, then, as I understand it, you can either apply this so-called dilution test—

A. (Interposing) Procedure.

Q. (Continuing)—or procedure, or you can apply the so-called agar disk procedure?

A. Right.

Q. Now, with respect to the agar disk procedure, in your experience have you become familiar with this procedure?

[25] A. Yes. We have used this method, or I have used it personally for the past thirteen years. In other words, I have used the agar disk procedure for the past thirteen years.

As new antibiotics are approved by the Food & Drug Administration and these are incorporated in the paper disks, they become antibiotic disks at that time, and as these are forwarded to us we pre-test these with control organisms to determine their effect on a variety of clinical isolates or clinical germs.

The Court: Then you don't rely on the certification, do you?

A. Yes. Yes, we do, your Honor.

The Court: Completely?

A. No, not completely. We have our own controls within our laboratory as well, because during the shipping process the temperature may affect the antibiotic within the disk.

The Court: All right.

Q. (By Mr. Trumbauer, continuing) Over that period of thirteen years, then, have you become familiar with the various companies or products that are in this field of sensitivity disk production?

A. Yes. We attempt to evaluate the products of two, three, or more companies. As these are prepared and are sent to me, we attempt at least to screen and do some initial survey of the [26] product.

Q. As well as the use of the products in your normal, everyday procedures?

A. Yes.

Q. Can you give us some idea of the various companies that you became familiar with in this field?

A. Well, we have tested the products of three companies. Should these be named?

The Court: Not if you don't want to.

What you are actually telling us is that the Henry Ford Hospital has a preferred list of vendors in this field; is that it?

A. We attempt to evaluate the products of several firms.

The Court: And out of that evaluation, you arrive at a list?

A. Yes, we select those that we consider to be better ones.

The Court: That is the way they run the plant out there, too. The purchasing department has a list of vendors that are preferred.

Q. (By Mr. Trumbauer, continuing) I am not trying to get into particular vendors you use at the moment.

The Court: Well, it would be an ad that might be worthwhile.

Q. (By Mr. Trumbauer, continuing) In terms of your experience [27] in this field, of knowledge of the sensitivity disk area, whether you have become familiar with the product of any of the companies that manufacture this.

A. Yes.

The Court: Don't misunderstand me. I think the practice is commendable myself.

A. I understand. We routinely on many products try to set up our own quality control standards.

Q. (By Mr. Trumbauer, continuing) No. I just want to know if you have become familiar with the products of any of the companies who manufacture these so-called sensitivity disks?

A. Yes, we have become familiar with them, but we have not checked all of them out exactly as one might—

Q. (Interposing) Well, have you become familiar to the extent of having checked any of them out? Which ones have you had an opportunity to check out over the years?

A. You do want the names of the companies?

Q. Yes. Not necessarily the ones you are using now, or anything like that.

A. We have tested products prepared by the Difco Company; by Baltimore Biological; and Consolidated Laboratories, as well as some from Case.

Q. I see. Now, in this area of these products that you have mentioned, do all these companies that you have mentioned [28] produce what is known as a sensitivity disk?

A. Yes. What can be considered as a disk or combination of disks.

For instance, the Difco Unidisk contains several of these disks in a ring form.

Another company prepares individual disks, and these are dispensed with a mechanical dispenser.

Q. Which company is that?

A. A dispenser is an article which holds eight cartridges and dispenses one of each by tripping a lever onto the plate. Rather than adding each disk onto the plate, eight are added at one time by tripping this lever.

Q. Which company is that?

A. This is Baltimore Biological Company. And the Consolidated product consists of a cloverleaf-type of disk where there are several disks on the cloverleaf.

Q. Showing you part of Libelant's Exhibit No. 1, can you identify that with respect to your background and experience in analyzing these various types of sensitivity disks? (Handing exhibit to the witness.)

A. Yes, we have tested these, but not in the detail that we have tested this company's single disk.

They produced disks of several concentrations, three concentrations per chemotherapeutic agent, and we had [29] much more experience with those than with these.

Q. Now, using that Libelant's Exhibit No. 1 there, can you tell the Court just how you, once you get this specimen from the physician, who has received it from the patient, just how you—

A. (Interposing) Perform the test.

Q. (Continuing)—perform the test, yes.

A. Very briefly, the organism is inoculated or transferred to the agar surface. As soon as possible, we place this unit on the surface, on the inoculated surface; replace the covered disk; place this into the incubator; and then between six and eighteen hours the plates are removed from the incubator and we look for zones of inhibition; in other words, the organism or germ growing on

the media, and if the drug or chemotherapeutic agent is effective, no growth will appear around the disk.

This means that the antibiotic, the agent contained within the disk, has diffused out into the media and has inhibited, prevented the organism from growing in that area.

This means that the organism is susceptible or sensitive to that particular drug.

And these reports are sent on to the physician.

The Court: And then actually, summed up, the result of that test tells you that this is the drug that the [30] physician should use or—

A. (Interposing) It does.

The Court: He doesn't have to.

A. Yes, this is correct. More specifically, we say this is a guide to chemotherapy. And the physician frequently has a choice of which antibiotic to use, and, with his clinical knowledge, he is better able to select the most efficient drug for treating that particular disease.

Q. (By Mr. Trumbauer, continuing) In other words, the physician, then, does utilize this in making his ultimate determination of what drug to use upon this patient that he is treating?

A. Yes. He uses, evaluates the information which is given as a result of the susceptibility test; he evaluates that very critically; and in our hospital his decision is frequently based on the antibiotic test report that he receives.

In our area I may go even further to state that the infectious disease section, that section which is most concerned with the treatment of all infectious and communicable diseases—that staff comes into our laboratory each day and evaluates much of the data on their patients.

In other words, they are very concerned as to what the organisms are and what their susceptibility patterns are so that they can best guide their therapy on the basis of this information.

[31] The Court: Well, you have a complete staff of resident doctors there, don't you, at Ford?

A. Yes. We have the staff plus the residents.

The Court: Yes.

A. Permanent staff and resident staff. And there are more than five hundred doctors on the staff at the present time.

We see somewhere between twenty-two hundred and twenty-eight hundred patients on the average day in the out-patient clinic, and we have one thousand and fifty beds for in-patients there.

Q. (By Mr. Trumbauer, continuing) And this is where you draw the various—

A. (Interposing) Clinical specimens.

Q. (Continuing)—clinical specimens?

A. Yes, sir.

Q. And the staff then comes into your lab and uses this information as part of its treatment of the various diseases?

A. Several of the medical specialties and several of the surgical specialties send representatives to our laboratory to follow up some of this information.

In the case of infectious diseases, they make daily rounds into our laboratory. Others make the occasional visit. And still others use the telephone to communicate with us.

[32] Q. Now, as a bacteriologist and microbiologist, can you tell us what you consider to be the definition of "disease"?

A. "Disease"? This, as you all are aware, encompasses a great deal of scientific information, but, very briefly, it involves a departure from the normal physiological state which we refer to as "health." In other words, if we have changes which can be termed either physical or chemical in the individual, we have a condition known as "disease."

Now, more specifically, since I am primarily interested in infectious and/or communicable disease, if an organism invades the body and that organism is a pathogen, and it has some virulence, which means it has the ability to destroy human tissue upon multiplication, then we term this an infectious disease.

Q. And specimens you receive particularly in your area

of communicable diseases do relate to what you consider to be disease in man?

A. Yes. This is well accepted by the medical profession, that many of the organisms which we isolate are evaluated as pathogens, depending on what site the specimen is obtained from.

In other words, if it is from the oral flora, if it is a specimen of sputum, there are organisms which are normal to healthy individuals. There are also other organisms [33] which are pathogenic.

The Court: Well, Doctor, I don't like to butt in here, but you will never get anywhere if you don't ask questions.

Will you give a special dissertation on a sample of sputum that was delivered to your laboratory as it might pertain to tuberculosis, and use that, and let us know what might come out of it?

A. All right.

The Court: Could you do that?

A. I would prefer to use streptococcal sore throat as an example.

The Court: All right.

A. Tuberculosis is a little more specialized.

The Court: This is an infectious disease, that throat condition?

A. Yes, it is.

The Court: All right.

A. Now, if we are given a specimen of sputum from a patient who has a sore throat—and this specimen can be either sputum and/or a throat swab, which means a cotton swab which has been touched on the throat—then this specimen is plated, inoculated onto the agar plate as we indicated previously; incubated for an eighteen-hour period; and the next morning we observe the plate microscopically, which [34] means that we look at it with transmitted light, and if we see that the isolates have a particular type of morphology and have hemolysis, a breakdown of the red cells around a particular colony, then we make a microscopic preparation on a slide.

We transfer the organism to a slide, and then we look at it and we make a tentative diagnosis that we may have

what we call a beta hemolytic streptococcus, which is the cause of septic sore throat and may be the cause of rheumatic fever; and that, if these are present in large enough numbers, then they may be the real cause of a patient's disease.

Occasionally we find carriers who have a few organisms. About two per cent of the general population may have an occasional organism of this type.

Having made this presumptive diagnosis within an eighteen-hour period, we isolate that organism—in other words, we transfer that organism into two mls. of broth in order to disperse the many cells that we have transferred and then we take a cotton swab and place it into the broth containing this isolate, streak it, transfer it onto a plate, and then we add the disk, particular disk we are using; incubate that for another eighteen-hour period, or in some places we can read the plates early—six to eight hours.

[35] The Court: With the disk.

A. With the disk. And you read out the zones of inhibition, and wherever you have these inhibitory zones, then you grade the organism as being susceptible, moderately susceptible, slightly susceptible, or resistant, depending on the approximate size of the zone. And the size of the zone varies depending on the amount of inoculant you have added, the typing media, and the antibiotic. Within certain ranges, the zone size does mean a little.

Q. The size of the zone can be one of the determining factors in susceptibility?

A. Can be interpreted as a semi-quantitative procedure, if one follows the direction of Anderson, who is one of the proponents who uses low-potency disks; and Kirby is another—who uses high-potency disks.

In other words, these disks have various amounts, and if you consider two potencies, those that have a graded low-potency amount—let us take, for example, penicillin may have two micrograms per ml. of antibiotic, and another may have ten micrograms per ml. The low-potency would be the two and the high-potency would be the ten.

And within certain limits, if one follows the procedure, or one which I have recently defined in the last year or

two, some interpretation as to degrees of susceptibility [36] can be made.

* * * * *

[37] Q. Can you tell us from looking at this disk which of these disks are antibiotic and which, if any, are not antibiotics?

A. Yes. Sulfadiazine is one of the sulfonamides and technically is referred to under the broader classification of a chemotherapeutic agent.

Q. That is the square disk?

A. That is right. The others, in order, are: terramycin, erythromycin, tetracycline, streptomycin, aureomycin, penicillin, and chloramphenicol.

These fall under the category of "antibiotics."

The Court: Does that mean each is an antibiotic on the disk?

A. Each is, except for sulfadiazine.

The Court: Except one.

A. They are all chemotherapeutic agents or drugs, in terms of usage in our field.

Q. (By Mr. Trumbauer, continuing): Now, you have indicated that in your opinion this article, Exhibit 1, is used in the treatment of disease; am I correct?

A. Yes.

Q. As a guide?

A. Yes. The information that we get or obtain from these disks and give to the clinician is used as a guide in chemotherapy.

Q. Based upon your experience, does this article have any value [38] with respect to what you—is it used in what you might term the diagnosis of disease?

* * * * *

A. * * * If the suspected organism is inoculated again onto a plate, and bacitracin disks are so placed on the plate and incubated for a period of eighteen hours, and the organism [39] shows susceptibility to this particular disk, then our presumptive diagnosis or presumptive identification is that this is a beta hemolytic strep belonging to the Lancefield Group "A".

Another example would be the hydrocuprein disk, in which this compound is incorporated in the disk. It, in turn, is used in the same way as I have described for bacitracin. It is placed onto an inoculated plate containing suspected colonies of pneumoccus, the organism which is a very common cause of pneumonia, and, if the organism is sensitive to hydrocuprein, the tentative diagnosis here is that it is likely a pneumococcus, provided that microscopic and one or two other tests have been done.

Q. I see.

A. So disks are used in the tentative diagnosis of the isolates.

Q. Would that include the Bacto-Unidisk?

A. Well, it doesn't include them as they are here. You get suggestive evidence here.

For instance, if you have a resistant staphylococcus which is colored orange, and it is resistant to penicillin, it is one of the more resistant types of staphylococcus aureus.

Q. What about the use of these sensitivity disks in the cure of disease? You have discussed treatment. Can you differentiate [40] treatment from cure?

A. The disks are not, as you well know, used directly in treatment of disease.

Q. Yes.

A. The information that we obtain from performing susceptibility tests using the agar disk procedures is used by the clinician. He weighs the evidence, the clinical evidence, and the laboratory data obtained by these testing methods, and then uses his good judgment as to which drug will be best for treating the patient.

So, I reiterate that the tests are a guide to patient therapy.

Q. Which would include both treatment and cure.

A. Yes.

Q. How about the area of prevention of disease? Does the information gathered from these disks have any value in the prevention of disease?

A. Yes. We use these indirectly in epidemiologic evaluations. One recent study involved some six hundred cul-

tures that we performed in the operating room area—the majority were done in the operating room—where cardio-vascular or open-heart surgery was performed. We tested airborne contamination. The majority of the organisms which were isolated belonged to the group known as staphylococcus albus.

[41] Since we know this organism is capable of producing heart disease, producing valvular disease of the heart valves, we were particularly interested in knowing whether these organisms were penicillin-susceptible or penicillin-resistant, because we had two deaths in recent months and we were particularly concerned to know what numbers of the airborne organisms were resistant to penicillin.

And our findings, using antibiotic disks, showed us that some forty per cent of several hundred strains isolated were resistant to penicillin, and this meant that we had to alert the surgeons to the fact that, since these are long operations and there was a strong possibility of organisms settling out on instruments, and sutures, and the prosthetic valves, the artificial valves, that these must be covered and transferred immediately as soon as possible into the operative site.

So the antibiotic disks warned us that we were dealing with a fairly virulent organism as far as this particular type of procedure was concerned.

Now, this is a special area in prosthetics or artificial surgical apparatus. These problems are not quite as great in the field of general surgery. But in this instance it has real epidemilogical value.

[42] Then there is the other area that some of us are familiar with. Bacteriophage types, such as 80, 81, are considered frequently to be the hospital—so-called hospital strain of staphylococcus that is responsible for a good deal of disease. And, if our susceptibility tests show that the staphylococcus is resistant to penicillin and tetracycline, we have suggestive evidence that this may be one of these phage types.

So they can be used as aids in the diagnosis of epidemiology problems.

Q. Are the various disks which you indicated you have familiarity with, namely, the Bacto-Disks, Exhibit 1,—is the use to which you put this disk, to which this disk would be put in this sensitivity testing area you have described, similar in its application to the disks produced by Consolidated Laboratories and Baltimore Laboratories, which you have indicated?

A. They have the same general purpose. They only vary in certain specifics, methods of handling.

These disks are smaller, for instance, than those of Baltimore Biological, so the zone size varies.

You have to standardize the zone size, using this disk, against zone sizes produced by slightly larger disks.

[43] The ones which I use are from 6½ to 7 millimeters. These, I estimate, are probably 3 to 4 millimeters.

So there is a slight difference in methodology here, in technique.

Q. But basically they all contain the antibiotic?

A. Yes. They operate on the same principle.

Q. Doctor, are the views you have expressed in your testimony here in accord with the views of your professional colleagues in this field?

A. According to my experiences throughout the past thirteen years, it is my considered opinion that there has been improvement in the quality, very definite improvement in the quality of antibiotic disks since initial certification,—since the requirements were made to have the disks certified.

We were much disturbed in the field and there was great controversy within our group, and this situation was also observed by the clinician, that there was too much disparity between the tests performed by one individual using a certain type of disk and another individual, and frequently within the same laboratory using different types of disks there was great variation, especially between the period 1954 to 1957, at which time I was very interested in evaluation programs using different types of disks.

[44] Q I was really just trying—I didn't want to lead you astray there. I was just trying to determine

whether the views you expressed with regard to the use of the antibiotic disks—

A. (Interposing) Is acceptable?

Q. Is in accord with the majority of your colleagues in the field?

A. Yes. Very definitely, the large majority of individuals concerned with diagnostic microbiology feel that the antibiotic disk procedure is a very valuable tool for both the microbiologist working in the laboratory and the individual interested in treating disease. The majority of people find this very helpful.

[45] *Cross Examination*

By Mr. Williams:

Q. Dr. Truant, I believe you said that you sometimes used the disk test for diagnosis of disease, or at least the information from the disk is used as a part of diagnosis. Would you define "diagnosis" for me? I am afraid I am a little rusty on that, if I ever knew what it was.

A. Diagnosis is the process of arriving at a decision as to the cause of disease, related in this discussion to the patient. So it is the determination of the causative factor or factors in the disease process.

Q. Do physicians in your experience, in your laboratory, use various and sundry sources of information to arrive at a diagnosis?

A. Yes.

Q. What would some of those be?

A. Well, their clinical experience; submitting specimens to various specialties in the department of laboratories, such as the Hematological or Blood Division, the Chemistry Division, Bacteriology Section.

They use a third very useful method that is referred to as radiological procedure, or taking X-rays.

These are the three main procedures.

Q. Do they sometimes refer to literature or textbooks for [46] background information?

A. Certainly.

Q. In arriving at a diagnosis?

A. Certainly.

Q. You referred to the possibility—I believe you said tentative identification of an organism in connection—

A. (Interposing): Yes.

Q. (Continuing): —with the agar disk test?

A. Yes.

Q. Now, you do not mean to say that identification of an organism, or certainly not a tentative identification of an organism is a diagnosis of disease, to you?

A. No. But this assists in the final diagnosis. But this is one step.

Q. Like the other information which you just described?

A. Yes.

Q. It is in a similar category; is that correct?

A. Absolutely. Yes.

Q. You referred—I will ask you: Did you not refer to several procedures, several laboratory procedures, which fall within the general category of sensitivity or susceptibility tests?

A. Yes. There are several types.

Q. Would you mind mentioning those again? I am not sure I got all of them. I believe you referred to four. Is that correct?

[47] A. Yes. The one most widely used, according to my experience, is the agar disk diffusion procedure.

Q. Is that the one which has the disk we have here—

A. (Interposing): This is the one under discussion.

Q. (Continuing): —the exhibit?

A. Yes. The second one which is rather widely used, and is rather time-consuming, is a tube dilution procedure.

The other is the incorporation of the drug in agar media.

Now, by "agar," we can think in terms of something like jello. It is a solid menstrum culture media, so that there are individuals who can test the susceptibility by adding the drug to the agar when it is in the fluid state at forty-five degrees centigrade or slightly higher, and then letting that solidify. It means they have incorporated the drug within the agar media. And, upon solidi-

fication, they transfer the organism onto the surface and see whether the organism grows at that concentration.

Q. Is there anything resembling a zone of inhibition in that procedure?

A. In that, usually it is an all or none. No.

Q. Just growth or no growth?

A. That is right.

Q. Is that sometimes referred to as the agar plate test?

[48] A. Yes. But I must qualify this. This is also an agar plate test.

Q. Except it uses a disk?

A. Yes.

Q. In addition to the agar, the inoculant, and the drug?

A. That is right. The fourth one, if you will permit me to finish, the fourth procedure, which is also used rather frequently, is the addition of antibiotic to a strip of filter paper, and these can be crosshatched. Filter strips containing different antibiotics or different concentration of one antibiotic can be crosshatched and added to the surface, inoculated agar surface, and incubated.

Q. What do you mean by "crosshatches," "crosshatching"?

A. "Crosshatching" is laying one strip over the other.

The Court: Like you make a cranberry pie.

A. Yes.

Mr. Williams: The way I make one, Judge!

A. So those are the four I mentioned.

Q. (By Mr. Williams, continuing): Now, let's take the agar plate test without the disk. Is it your opinion that the agar plate and the agar, the inoculant, and the drug which are employed in that test, are used as a—I believe you used the term "guidelines" for treatment?

A. Yes.

[49] Q. In other words, you would say that to the extent that the disk, agar disk test, is a guideline to treatment, that the agar plate test is?

A. Yes.

Q. They may not be in the same area of accuracy, but—

A. (Interposing): This is right.

Q. (Continuing): —similar?

A. That is right. The procedure—the agar plate procedure does not have the facility that one has with the disk procedure.

Q. Well, to clarify it for me, and perhaps some others still more, you are not testifying, as I understand it, that the plate and the agar and the other constituents which are used in the procedure, or the disk, is used itself in treatment, but it is the result of this test which is one of the guidelines which the physician may look to?

A. Yes.

Q. Is that correct?

A. Yes.

Q. Would you say the same thing about the test involving the impregnation of a strip in the crosshatching?

A. Certainly.

Q. And the same thing about the tube dilution series?

A. Certainly. That the information obtained from these procedures [50] is used to guide the physician in his therapeutic program.

Q. As one of the guides?

A. Yes. I might add that it is a frequently-used guide. In other words, that a large percentage of the specimens that we obtain, on which we have requests, a large percentage do request that we run susceptibility tests by this procedure.

The Court: You said one of the guides that is used by the physician in his therapeutic what?

A. Regimen or treatment program.

The Court: All right.

Q. (By Mr. Williams, continuing): Dr. Truant, did you not state that in the tube dilution procedure you were running that you may have a series of tubes containing one milligram, or microgram?

A. Yes.

Q. Five micrograms?

A. Yes,

Q. Ten micrograms?

A. Yes.

Q. And one milliliter of the—

A. (Interposing): No. This was the concentration per milliliter.

Q. Per milliliter. Yes.

A. Per milliliter. The concentration per milliliter. You may have any volume. You may have per test tube, you may have [51] a volume of two mls., six mls., ten mls., or larger volumes, or less volumes in tubes. Some people use the procedures where they only apply half a cc.

* * * *

[53] Q. Dr. Truant, would you tell me again, is your laboratory properly described as a microbiology laboratory?

A. Yes. It is a clinical microbiology laboratory, or some people use the term diagnostic—clinical diagnostic microbiology.

Q. What kind of tests do you do other than the four sensitivity tests which you have detailed to us?

A. You mean what other types of susceptibility tests?

Q. Not just susceptibility tests. In laboratory testing generally?

A. Well, our department is divided up into, first, the blood service, and on this service we test blood cultures.

We do bacterial serology, which means testing serum for various types of human bodies. Antibody tests.

We have the urine service, on which we test urine submitted from patients suspected of having significant bacteria—significant urinary tract disease.

We have a routine service, on which we handle a large variety of clinical specimens other than those mentioned, specimens such as throat, sputums, abscesses, tissue specimens from the patient, et cetera. And on this service we do tests for both bacteria and fungi.

[54] We have another laboratory that just does tuberculosis work; the isolation of acid-fast organisms commonly referred to as tubercule bacillus, from all types of specimens from humans.

We have another service which just handles stools, fecal specimens for the isolation and identification and susceptibility testing of pathogens.

We have another service that handles the aerobic, special aerobic, anaerobic and fastidious microorganisms. And then I have several people on research programs.

Are you interested in me listing those?

Q. No, sir. I am quite satisfied. What I wanted to ask you was whether you would again affirm that the information which is obtained by you and passed on to the physician from these various testing procedures is one of the sources—one of the types of information that the physician employes in making his diagnosis of a particular disease? Is that correct?

A. Yes.

The Court: Well, before you get to that particular point, in any of those procedures you have just outlined, do you, or anyone else in your laboratory, make an actual diagnosis in relation to the patient yourself?

[55] A. We assist in the diagnosis.

The Court: That wasn't my question.

A. No, we don't diagnose the patient's disease.

The Court: All right.

Q. (By Mr. Williams, continuing) You assist in the manner in which you have described, namely, running these tests and making reports of your findings?

A. Furthermore, we do consultation work. You see, the clinician comes in to discuss the problem with us, and we discuss the various clinical aspects. So we do frequently assist in diagnosis. But the clinician is primarily involved in the final answer.

But we have a very close rapport with the clinicians throughout the hospital.

Q. Dr. Truant, when you get a zone of inhibition showing some retardation or stoppage of growth around the disk in this particular type of procedure, what significance—I will change that.

I should like to ask you at that point, can you use that result to advise the physician what the dosage or concentration of antibiotic which he is going to administer to the patient, if he is going to do it, he should use?

A. From experience, only on a very broad basis. We

only tell [56] him whether the organism is susceptible, moderately susceptible, slightly susceptible, or resistant.

There are reports in the literature where they draw that parallel that you are asking me. But unless you have tube dilution information, it is merely a qualitative answer. We don't propose it to be quantitative.

But some people do use it as semi-quantitative.

Q. It is fair to say that unless you have other information before you perform the test—the agar disk test—that then you can't make any quantitative decision on this point that I asked you as to what concentration should be given to the patient? You must have some other information other than that obtained from the disk test?

A. No. No. Very frequently the clinician makes his decision just on the basis of the disk information.

We only go on and do quantitative determinations in the case of blood isolates.

But usually the information obtained from disk testing is passed on directly to the clinician and he draws his conclusion based on company recommendations as to what dosage he should use.

Q. That wasn't my point, Doctor. I am sorry. I didn't articulate very well.

I meant that in order for you in the laboratory [57] to make an informed guess as to what dosage should be used of a particular substance to be administered to the patient, you must have some information in addition to the information that you obtained from the sensitivity test?

In other words, the zone of inhibition itself is not going to tell you how much the physician should give the patient, assuming he decides to use this antibiotic?

A. Not in itself.

Q. Yes. Now, Doctor, you, I think, in some manner which wasn't quite clear to me, and I would like to ask you: How do you incorporate into this area of the use of the disk, or the information from the disk test as a guideline for treatment, the matter of prevention? How do you incorporate that into this case?

A. Well, there are several aspects here. One or two I can mention.

One is that in treating the patient, let's say for staphylococcal disease, that you would reduce the number of individuals who are carrying this pathogenic organism and, therefore, you prevent the spread of disease on this basis.

A second very important aspect here is to ferret out sources, possible sources of contamination within the hospital area; checking out water; various pieces of apparatus, equipment, respirators, and what have you, [58] throughout the hospital.

By so doing, we prevent the spread of infection to both the sick and healthy within the hospital community.

Q. Are you saying here again that it is information which you obtained from these tests—

A. (Interposing): From those specimens.

Q. (Continuing): —which gives you some kind of guideline toward prevention of disease?

A. Yes.

Q. Is that what you are saying?

A. Yes.

Q. I am sure you are aware of the use of so-called economic poisons, or pesticides of various sorts?

A. Yes.

Q. To swab floors, furniture, and clean the hospital generally?

A. Detergents.

Q. Detergents and the like?

A. Yes. Not pesticides within the community, nor insecticides.

Q. I should have limited myself to economic poisons. But many of the substances or chemicals are used for that purpose; is that correct?

A. Yes. On floors—we are talking about floors and walls.

Q. Floors and walls.

A. Not aerosols. They are only occasionally used in our hospital [59] area.

Q. Would you also say that the use of these substances aids the prevention of the spread of disease?

A. Yes.

Mr. Franchino: Objection, your Honor.

The Court: Why?

Mr. Franchino: I think it is irrelevant if it is one of the articles which may or may be used in the prevention of disease. We are talking here about sensitivity disks, and in particular the Difco product, the Unidisk.

The Court: Well, he has given here, as an element of the prevention that is involved in his answer, reducing the number of persons that are carrying the organisms and thereby to prevent others from getting it.

When my mother told me, when I was a kid, to stay home from school because I have a cold, she is preventing the spread, too.

It is all-embracing, I would think—that type of prevention.

I think he has a right to question the doctor on just what he means by the prevention that he has indicated by reason of these guidelines.

The Witness: Should I go ahead and answer this?

[60] The Court: Yes, sir. Please.

A. Prevention means control of the spread of disease. And very obviously there are a number of methods whereby we achieve this end.

Adding disinfectants to floors does help to reduce the bacterial count.

Q. (By Mr. Williams, continuing): That is the object of the procedures which you have been describing with the use of antibiotics—of disks?

A. No. I was not relating this to airborne. We do not recommend the addition of antibiotics to control airborne infections.

Q. But you do test quantities of hospital nurses and personnel generally to determine—

A. (Interposing): Yes, sir.

Q. (Continuing): —whether they are carriers of, say, some staphylococcus of an infectious nature?

A. Yes, sir, we do. I just don't want the point confused that we are using aerosols to reduce the incidence of disease in air or on floors.

Q. Doctor, how do you relate the use of the information from the disk test to the cure of disease?

I believe you did mention that cure had a place in this picture.

[61] A. Yes. The information that is gained from the use of the disk procedure is of tremendous value in choosing the right drug without allowing a large element of chance to take place, because there are many strains of staphylococci which are resistant to one or more drugs, and the clinician would have to, by trial and error, use one and then another when the previous one had failed. And the cure rate, as you well know, has been much higher since the advent of antibiotics, and we have appreciably reduced the length of stay of patients with specific disease because of antibiotic treatment. And it is well understood within the hospital community that the antibiotic testing procedures have aided greatly in the treatment and cure of disease entities.

* * * *

[65] Q. (By Mr. Williams, continuing) * * * I will merely ask him whether in his experience, with his background, he can say whether—if I came to him with this high fever and a disease which looked to a physician as though it required an antibiotic, whether in his experience the physician would prescribe the antibiotic and then take the specimen and send it for the test?

The Court: Does the chart come to you when the sample comes to you?

A. No, it does not. The teaching along this vein in our hospital [66] is that you take the specimen first and then administer the antibiotic. This is the infectious disease teaching of this aspect of the case.

Q. (By Mr. Williams, continuing): No matter how—

A. (Interposing): Yes, no matter—

Q. (Continuing): —how in extremis the patient is?

A. Yes. Because you can take two or three blood specimens within a half hour to an hour and a half. Within very short intervals.

Q. You are talking about blood specimens and I am talking about antibiotic sensitivity.

How long did you say it took to conclude the tests? About eighteen hours, did you not?

A. I think we misunderstood each other. You said would I give antibiotics first and then take the specimen?

Q. That is correct.

A. No. I would take the specimen first, and then the clinician will administer antibiotics.

Q. I see. I see the misunderstanding. I was thinking of the specimen in terms of a specimen from which you would obtain an isolate for the sensitivity test.

A. Yes. You worded that correctly. You take the specimen and then you plate it. But you give the medication while all of this other procedure is going on.

[67] You take the specimen. I go to your throat and take a throat swab. I have collected a specimen. And then the antibiotic can be administered by the physician.

Q. Without waiting for the result of the sensitivity test?

A. Oh, yes. We just misunderstood each other.

Q. We certainly did.

A. Yes.

Q. Undoubtedly, I did not ask the question very clearly.

The Court: What happens if the disk that is used in the culture is a disk that indicates some other type of antibiotic? Do you change?

A. Then they switch their therapeutic program, yes, sir.

Q. (By Mr. Williams, continuing): May I ask this: Would they switch the therapeutic program if the antibiotic being used was successful?

A. No. Very likely not.

Q. Would there be considerations other than the results of the sensitivity tests which might influence the doctor not to switch, namely, the sensitivity of the patient to the particular antibiotic indicated by the test?

A. Yes, sir.

Q. Might not there be a number of other factors which would influence the doctor not to switch or go to a different antibiotic than that indicated by the test?

[68] A. Yes, there are various reasons.

Q. Doctor, am I correct in my assumption that in your laboratory you deal only with tests on organisms obtained from human beings?

A. No. We also do some outside consultation work. For instance, if it is an oil specimen from one of the factories that may be implicated in producing corneal infections, eye infections, then we will also test that.

We will test food, frozen egg, that come into our department.

We do other types of bacteriology survey as well.

Q. And are these tests sometimes used on organisms taken from animals and from plants, to your knowledge?

A. The antibiotic susceptibility?

Q. Yes.

A. Not within our area.

Q. Not within your area?

A. No. We are not concerned—

Q. (Interposing): You don't know whether that is done or not?

A. Yes. It can be done in veterinary matters, but it is not widely used.

Q. Doctor, you testified, I believe—correct me if I am wrong—that Dr. Anderson used a low potency disk and [69] Dr. Kirby uses a high potency disk?

A. Yes.

* * * * *

[77] Detroit, Michigan,
Tuesday, May 18, 1965,
2:00 o'clock P. M.

(Court convened pursuant to the adjournment.)

Mr. Trumbauer. The Government will call Dr. Charles Wolfe.

DR. CHARLES K. WOLFE, JR. was thereupon called as a witness on behalf of the Libelant and, having been first duly sworn, testified as follows:

Direct Examination

By Mr. Trumbauer:

Q. Your full name, sir?

A. Dr. Charles K. Wolfe, Jr.

Q. And your address?

A. Office address, 636 Church, Evanston; home address is 909 Central, Wilmette. Both in Illinois.

Q. And what is your profession, sir?

A. I am a physician.

Q. And in particular do you specialize in any particular area as a physician?

A. I have qualified as an internal medicine specialist and have, [78] styled myself as a subspecialist in infectious diseases, since there is no such recognized specialty there.

Q. And are you connected in this area with—in addition to your private practice—with any particular hospital or other medical group in connection with this area?

A. My faculty appointment is with the University of Illinois Medical School, and my appointment in the Department of Medicine is with the private practice hospital known as Presbyterian-St. Luke's in Chicago, Illinois. And this is the only private practice hospital in the very large—in fact, the world's largest medical center.

Q. And your work at St. Luke's is in what particular field?

A. In the field of infectious diseases.

Q. Can you give the Court and counsel some idea of your education in the field of medicine?

A. Yes. I went to the University of Pennsylvania Medical School in Philadelphia, and from there I had an internship in Chicago, following which I had a residency in St. Elizabeth's in Washington, and two years again in Washington—one as a Fellow in Infectious Diseases and one as a resident in general medicine. And then a final year of residency in Chicago, again in general medicine.

Q. Now, have you, during the course of your experience, been engaged either by yourself or with other professional men [79] in the publishing of any papers in any particular field?

A. Yes. They have all been confined to the field of infections, the treatment of infections, and in particular the use of antibiotics in infectious disease.

* * * *

[86] The Court: I think that should be defined, what his entire contract has been with the use of disks, so that we know whether he is talking about what somebody else [87] does or he does.

Mr. Trumbauer: Yes.

Q. (By Mr. Trumbauer, continuing): You have indicated you have utilized sensitivity disks from a laboratory standpoint as well as from the clinician's standpoint; is that right?

A. That is true.

Q. From the laboratory standpoint, in your experience do you know how this sensitivity disk is used?

A. I do.

Q. Just briefly, if you will tell us.

A. The sensitivity disk has a known amount of antibiotic impregnated in the disk, and this is then applied to a culture plate on which an organism has been applied and on which growth of this organism can be expected.

With the disk's antibiotic perfusion into the media on which the organism should grow, the antibiotic effect is then seen as an area where the organism will not grow.

This is the action of the disk with its antibiotic on the culture which I have taken from the patient and asked such a test to be done.

Q. And from a standpoint of you, then, as the physician now, going to your physician's role, which you have been involved in both ways, why do you send this culture to the laboratory [88] for this sensitivity testing? What is the purpose?

A. The purpose is for the establishment of a little better and more scientific basis on which to practice medicine and, in particular, to treat this patient and this disease.

Q. I see.

The Court: "Little better" and what, Doctor?

A. Little better medicine and more scientific basis for it.

Q. (By Mr. Trumbauer, continuing): Specifically then, Doctor, can you tell us how this procedure takes place? How are these disks used to enable you to better treat this patient you are dealing with?

A. The disks are manipulated in the laboratory and readings are made from these disks, and they are placed on a report which is in answer to my request that disk sensitivity readings be done on the culture that I have sent to the laboratory.

And in our particular institution the report comes back to me as "S" for "sensitive"; "X" for "sensitive with persistent colonies"; and "R" for "resistant."

Those are the only categories in which this has been reported to me.

Q. And once you get that information, that specific information, what do you do with it as a physician?

A. First and foremost is to note the reaction to the particular antibiotic which I have—if I had to—placed the patient [89] on because of the emergency of this situation, and if this proves to be sensitive I am satisfied that this is the effective treatment and will effect a cure.

If it proves by this test to be resistant, I will then choose a different antibiotic, one that is marked "S" on the report, hopefully. This would constitute good medicine.

* * * *

[91] Q. How many of these tests are performed in your hospital, say, in a given period of time? Perhaps a week.

A. Well, I am told that the volume of disk sensitivity testings in our hospital is approximately five thousand per month.

Q. Per month?

A. That is correct.

Q. And based upon your experience as a physician and having the laboratory experience, to what extent are these tests relied upon? We are in the treatment area now, the treatment of disease.

A. Well, I would say they are the main basis of reliance as judged by the volume of the numbers of tests that are performed in comparison to the more precise testings that take longer, and which, by the way, were the basis for the scientific publications which I have listed on my curriculum vitae.

Q. Could you describe for us just very briefly these other methods which you say are less used, you might say, in this sensitivity program?

A. I guess we would have to put disk sensitivities as one of the three major ones that are used. No. 1—four major ones, excuse me.

[92] No. 1 would be the phenomenon of typing the organisms directly, and this requires the preparation of a typing serum and also watching the response of the organism under the microscope when it is bathed in this typing serum to see the phenomenon known as "Quellung." This is a capsular swelling phenomenon, and this gives immediate information. But, unfortunately, many bacteria do not oblige with this phenomenon, and the typing serumis very often unavailable, extremely expensive to produce, and short-lived if it is available.

The second, and by far the greatest use of antibiotic information, is the disk sensitivity, and this accounts for fully ninety-five percent of the antibiotic experience that a hospital laboratory will report in relationship to any particular organism that it has been called upon to isolate and identify.

Q. That is the disk that you have—the procedure you have just described for us in relation to Exhibit No. 1?

A. That is correct. In rare instances, where there is a dispute about the number of—about the actual disk results, or if the patient fails to respond the way the disks indicate that the patient should respond, we can then resort to a more precise method known as a tube dilution sensitivity, and I might add that this was the means by which the disks actually were [93] checked on, or put on a firm footing originally, according to my understanding of it.

And this is resorted to in rare instances, in more serious infections where the facts do not fit the clinical course of the patient, or his response or lack of it, to the antibiotic.

And the fourth method, of course, are the serum methods. This is referred to in the typing of streptococci as precipitating M-protein or specific cellular components.

Q. What about the addition of the antibiotics to a filter paper? Does that come within one of the definitions that you have described here?

A. As far as I know, this is not practiced in our—

Q. (Interposing): In your hospital?

A. In our hospital.

Q. Now, is the antibiotic which is impregnated on that disk the same antibiotic which you as a physician, as a result of that disk—as a result of that testing—might eventually use upon the patient?

A. To my knowledge, it is.

Mr. Williams: Your Honor, may I have the question repeated and the answer?

The Court: Yes. Will you repeat the question, [94] Mr. Buckey?

(The last question and answer were thereupon read by the Reporter.)

The Court: Without being facetious, Doctor, you wouldn't administer it in that state, though, would you?

A. Nor in that dose; no, sir.

The Court: No. All right.

Q. (By Mr. Trumbauer, continuing): You do not apply, obviously, the disk to the patient; is that right, Doctor?

A. It is a thought, but I wouldn't do it!

Q. Now, you have discussed this sensitivity treatment and the disk treatment to this test in connection with the treatment of disease, and I think you mentioned also the cure of disease? You used the word "cure" as you were discussing treatment?

A. I think the antibiotic choice is the thing I particularly used it for, and the reason I use antibiotics is to effect a cure.

Q. Yes. Would it be fair to say you utilize this information as a guide in the treatment, with your ultimate objective that you utilize it to effect a cure?

A. This is so.

Q. Is the disk test used in any way with respect to what might be termed "diagnosis of disease"?

[95] A. It certainly can be used as a rough screening measure, but not a precise diagnostic.

Q. By "diagnosis," as a physician what do you understand?

A. Well, to exclude Group "A" streptococcus from the other groups of streptococci, the importance of this being that Group "A" streptococci regularly produces a pathologic condition in humans, whereas the other groups do not.

Q. Then this sensitivity test can be at least of some use in certain areas?

A. This is so.

Q. In connection with the diagnosis of disease?

A. Yes. Another example would be whether or not the staphylococcus were penicillin-resistant, which has become a matter of great importance in hospital areas.

Q. And in your experience as a physician and laboratory man in this area, can you tell us whether or not, in your opinion, the disk can be used in connection with the prevention of disease?

A. I can't—

Q. (Interposing): Say, in a statistical sense or in some broad sense?

A. Yes, in a broad sense I can say that the analysis of the information which we are now getting from our computer, and compounded with the analysis that would be made of such [96] data from other areas, such as here, Seattle, Washington, and so forth, might be able to show you trends of the bacterial population and their susceptibility to a particular antibiotic that is used in that community.

* * * *

[97] Mr. Williams: Your Honor, may I ask for a clarification of that?

It is my understanding he has heretofore asked whether the information obtained from these tests is so utilized, and now he is asking whether the disk is so utilized.

The Court: I think you will have to develop that on cross-examination.

Mr. Trumbauer: I will rephrase that in view of your direct testimony.

Q. (By Mr. Trumbauer, continuing): Obviously, as I say you don't apply the disk directly to the patient, but the results that you obtain from the disk, the information—

A. (Interposing): As reported.

Q. (Continuing): —as reported, you would say primarily is used in the treatment area?

A. That is an accurate statement.

Q. And the diagnosis area would be of lesser importance?

A. That is so.

Q. And the prevention area would be of a lesser significance, although both would have some uses; is that correct?

A. Right.

Q. Or the results would have some usage in this area?

A. That is correct.

[98] Mr. Trumbauer: Your witness.

Cross Examination

By Mr. Williams:

Q. Dr. Wolfe.

A. Yes, sir.

Q. Without regard to the definition in the statute of the term "drug," do you, as a medical doctor, consider that sensitivity disks are drugs in the medical sense or the scientific sense?

Mr. Franchino: Object, your Honor, on the grounds of irrelevancy, in that the statute sets up its own definition of the term "drugs," and while we think it is perfectly permissible for the witness to state his understanding of the modifying terms "cure," "diagnosis," "mitigation," and "treatment," we don't think it is proper for him to usurp the function of the Court and the legislature in providing a definition of the term "drug."

The Court: The only trouble with that objection is that I think he has been produced here as a witness, as an expert, and it is the function of an expert, as here—as I understand the function of an expert in the trial of

any cause—to advise the Court and the jury—sometimes the jury is the Court—and I expect to get some [99] advice from the expert. So I would say the question would be a proper one.

Mr. Franchino: Thank you, your Honor.

Mr. Williams: Do you want the question repeated?

The Witness: Please.

Mr. Williams: Would you read the question, Mr. Reporter?

The Reporter (reading):

> "Q. Without regard to the definition in the statute of the term 'drug,' do you, as a medical doctor, consider that sensitivity disks are drugs in the medical sense or the scientific sense?"

A. I would have to say that it is drug usage in a scientific sense.

Q. (By Mr. Williams, continuing): You don't give them to the patient and you don't apply them to the patient, do you?

A. The substance, however, is the same.

The Court: You say—

Q. (Interposing): The substance is the same?

The Court: Wait until I get that written down here. That it was drug usage in the scientific sense or medical sense?

[100] A. In the scientific sense.

The Court: All right.

A. In the medical sense it would be that the substance is the same in the two cases, the disk and the drug.

Q. (By Mr. Williams, continuing): Are you saying—I am sorry, your Honor.

The Court: Go ahead.

Q. (By Mr. Williams, continuing): Are you saying, Dr. Wolfe, that when you—strike that.

When you refer to "substance," are you referring to the antibiotic on the disk?

A. I am.

Q. In other words, you are saying that because the antibiotic on the disk is a drug, that the disk is a drug? Are you going that far?

A. I am saying it is used in the disk and it is also used in the cure, so that the drug usage has a common ground in the scientific sense.

Q. Are you saying any more than that the information derived from these sensitivity tests is used as a sort of guideline in treatment, for example?

A. No. I think that would be a very fair statement. As a guideline. It helps the antibiotic choice to be given.

Q. To what extent are you persuaded by the fact that the disk [101] bears a substance which corresponds to other substances, namely antibiotics, which are commonly used as drugs?

A. I am swayed very much, and regularly swayed.

Q. Now I will go back again to where we started. Is it your basic concept that a drug is something which is administered to, say, individuals or animals, or applied to individuals or animals in some manner? Or shall we go even further and say it has some direct effect upon their bodily function?

A. Would you like me to say "Yes, I agree," or how can I help?

Q. I would like you to say what you think, sir.

The Court: You should never ask opposing counsel what they want you to say!

Do you want the question read again, Doctor?

A. Yes.

The Court: There may be two questions in one. I don't know.

The Reporter (reading):

> "Q. Now I will go back again to where we started. Is it your basic concept that a drug is something which is administered to, say, individuals or animals, or applied to individuals or animals in some manner? Or shall we go even further and say it has some direct effect upon their bodily function?"

A. I guess that is three questions.

[102] The Court: Well, there are at least two there that I recognize.

Mr. Williams: Let's take—

The Court (interposing): I think you should break it up.

The Witness: Please.

Mr. Williams: Let's take the first one.

Q. (By Mr. Williams, continuing): Does the term "drug" in the medical sense or scientific sense—I am not sure which one should be used here—shall we say in the medical sense, include substances which are administered to human beings for the treatment of disease, or the cure, or the mitigation, or something of that nature? It includes those substances?

A. This is a popular concept. However, a drug in the medicine cabinet is still a drug; it is not inside the human being.

Q. But it is intended for that purpose?

A. This is a popular concept of the word "drug."

Q. But if it is used for that purpose, then it is a drug? Correct?

A. That is correct.

Q. If this same substance were one which could be applied to the body as a salve to stop irritation or some other disease, would that be regarded as a drug?

A. Yes, I believe it could be.

[103] Q. Do you know of anything other than substances which are administered to human beings for these purposes—for this purpose—or which are applied to the body of human beings—I should add "or animals"—which is a drug?

A. My understanding of drugs, I will repeat, is that they are a class of substances; that if they have one phase of being used in the treatment of humans, they are still drugs.

Q. Suppose they aren't suitable for application or administration to the human being or the animal, are they drugs?

A. Yes, of course.

Q. What is an example of such a substance?

A. I think nicotine comes easiest to my mind.

Q. But nicotine is inhaled.

A. And it is absorbed after it is inhaled.

Q. So it goes into the body in some manner?
A. That is correct, sir.
Q. Let's see. Do you have an example of something which is not taken into the body or is not applied to the body which you consider medically as a drug?
A. I don't believe I can think of one offhand.
Q. Thank you. Doctor, am I correct in my understanding that you stated that when you are confronted with a patient who is ill from some infectious disease—I understand that is your practice—that you will use your clinical judgment [104] and other sources of information available to you to determine as best you can at that stage what his difficulties are, what his trouble is, what the diagnosis is, and then you will commence treatment in that case pending further tests? Is that correct?
A. Pending the outcome of the tests, yes, sir.
Q. Yes.
A. That is correct.
Q. Now, when you have received the information from this, or that, or another laboratory test, including these that we are dealing with here, do you just blindly go ahead and feed the patient the particular antibiotic which is shown to be resistant or susceptible?
A. I am focusing on the word "blindly"!
Q. I thought you would.
A. And I think that that would not be appropriate.
Q. Your answer is "No"?
A. No, I wouldn't be blinded by it.
The Court: What happens, Doctor, if the test reveals the use of penicillin and the patient is allergic to penicillin? What do you do then? Do you try something else, or go right ahead and give him the penicillin anyway?
A. No, we do not go right ahead and give the penicillin anyway. A definite clinical judgment has to be exercised weighing the [105] risk of penicillin reaction against the outcome of the patient if he is on a less desirable antibiotic.
This situation is fairly rare, however. There are usually several antibiotics that one organism would be sensitive to.

Q. Might there not be other reasons why you wouldn't use penicillin in this particular instance?

(No response.)

Q. Let me pursue it this way: Does the physician ordinarily have more than one antibiotic available to treat a particular infection, particular infectious disease?

A. I would say he always has a choice of more than one.

Q. Always has a choice of more than one?

A. Yes.

Q. So that to the extent that he always has that choice, the value of the information from the sensitivity test is somewhat reduced, isn't it?

A. Would you repeat that question, please? It did not sound right.

Q. Let me put it another way. You have several situations—I can think of two—where, in the first place, you have a number of antibiotics which are available, is this not so, for treatment of several types of infections, the broad spectrum type of antibiotics, so-called; is that right?

[106] A. This is correct.

Q. It is also correct that if you, using your clinical judgment and other sources of information available to you—your experience, the literature, textbooks—decide to administer a particular antibiotic to your patient, perhaps pending the outcome of tests in the laboratory, and that particular medication is satisfactory and works out well for the patient, then, when you are returned the report showing that another antibiotic is preferable, would you then change the medication?

A. That was a very long question, but I would not change it, and the reason for this is the fact that there are often more than one antibiotic to which sensitivity will be shown by these disks.

Q. Doctor, I believe that you stated that in connection which I perhaps missed, that in some cases your first procedure is to isolate and identify the organism which has been extracted from the patient?

A. Whenever practical and possible, this is the first step.

Q. How do you go about that? Just an example.

A. It requires the taking of a specimen, which is ordinarily performed after the examination of the patient and a particular focus on the area of major complaint.

I believe an example might be the sore throat example, in which case a cotton swab, sterile cotton swab [107] is introduced and touched to the patient's throat, and then brought back and placed either on culture media or into culture liquid, and sent with my request for identification and sensitivity testings to the laboratory.

Q. Now, excuse me. Who does the identification? Who carries out the identification procedure in this situation?

A. The paid employees of the hospital bacteriology laboratory.

Q. Is the identification procedure conducted simultaneously with, or before, a sensitivity test is conducted?

A. That comes on three ways. It can be done before; it can be done simultaneously; and it can come after the disk sensitivity has been reported or completed.

Q. Now, I just want to get this straight. I think we have it straight, but just to be sure, because it is an important point, let me ask you again:

Is it your testimony that it is the information from this particular test, the sensitivity test, which is used by the physician as a guideline to treatment of the patient?

A. This is absolutely correct.

Q. Is it the information obtained from this test which is used by the physician as an aid in diagnosis?

A. To a much lesser degree.

Q. Is it used in any sense as an aid to preventive measures?

[108] A. To an even lesser extent.

Q. Would you say that chemicals used to swab the floors and walls of a hospital are used in the prevention of disease?

A. I often order it in that guise. Whether it does or not is still being studied.

Q. Would you place—

The Court (interposing): You don't believe in the soap ads, then!

Q. (By Mr. Williams, continuing): Assuming it killed all of the staphylococci that otherwise would be around, would you consider that it was used in the prevention of disease?

A. The swabbing material?

Q. Yes, sir.

A. I think it has an indirect application to the prevention, or at least lessening the chances of disease.

Q. About like the information obtained from the sensitivity tests, more or less?

A. I don't think the information is equatable.

The Court: I think we will take a recess at this time.

(A recess was thereupon taken.)

Q. (By Mr. Williams, continuing): Dr. Wolfe, in making a clinical evaluation of a patient's condition, or, if you [109] prefer, in diagnosing his condition, from what sources in general would you obtain, or upon what sources would you draw to obtain the information which you bring to bear on this problem?

A. From many sources.

Q. Would you give me some examples?

A. Yes, I would be very glad to. I will carry on the example of the sore throat, which we used earlier.

The first thing is the history of the actual disease as told to the doctor by the patient. To make it brief, "My throat hurts me," or "I have a fever and my throat hurts," or some such sequence as that.

The second step is the physical examination, which presumably is complete but which also focuses on the affected part that the patient has complained about.

This will then be compared with the doctor's experience, and the numbers of throats he has seen before, and the numbers of times he has heard this complaint made to him, and he will then decide on a presumptive basis what is the cause of this sore throat; and, sizing the picture up, he will then ask that other tests be performed, confirmatory tests, diagnostic tests, and at the same time he will elect, or judge whether he should elect to treat im-

mediately or wait for these other sources of information to be utilized.

[110] And finally would be the treatment; the cause and effect, the cure.

Q. Thank you, Doctor. Did you hear Dr. Truant this morning when he enumerated a number of laboratory tests which were used in his laboratory, such as, I believe, urinalysis, blood tests, and the like?

A. I did not.

Q. You did not. Do you frequently, or do you from time to time, order various laboratory tests on the organisms which you obtain from the patient, other than sensitivity tests?

A. I would say in the rare instances I do order additional tests, different tests, or special tests on this organism.

Q. And when you order these other tests, then the information which you receive from the procedure which is followed by the technician is conveyed to you and you use that as another source of information in evaluating the condition of the patient?

A. This is true.

Q. There has been a reference to several types of sensitivity tests. They are all characterized as in the vitro tests in the laboratory; correct?

A. That is correct.

Q. Whereas, a test which may be run on a patient is an in vivo test; correct?

[111] A. In a very broad sense.

* * * *

[114] Q. What relationship is there between this particular test using this typing serum and the sensitivity test?

A. None. This is not known as a sensitivity test. This is an identification test.

Q. Did you—or did I misunderstand you—did you say that one of the most important sources of information in determining—in obtaining guidelines to treatment is the sensitivity testing procedure?

A. I did say that.

Mr. Williams: Thank you. That is all.

Mr. Franchino: Your Honor, I would like to renew the objection—and possibly explain a little better than I did my reasons for making it, if I may—to strike the various questions put to Dr. Wolfe by counsel, Mr. Williams, relating to his medical and scientific understanding of the term "drug."

Your Honor pointed out to me that, inasmuch as the witness is an expert, it is appropriate for him to shed light on this question.

Now, the analogy that comes to my mind, your Honor, is let us say an accident case. If we were to call a traffic analyst or safety analyst as a witness in a negligence case, we would not be able to put the ultimate question to him—

[115] The Court (interposing): I appreciate that.

Mr. Franchino: And the point I am trying to make is, I see no difference between this situation and the other, and my objection is based upon that type of analogy, your Honor. Just for the record.

The Court: Well, I appreciate the ultimate determination is for the Court and jury but in this highly technical field, why, the Court feels that any information that is available from the experts is going to be helpful in his determination. And I appreciate the fact that it still is a determination of the Court as to whether or not this article is a drug.

But I call your attention to the affidavit you submitted in support of your motion for summary judgment, the last paragraph (reading):

> "I have read the claimant's answers to the Government's Interrogatories Nos. 7 and 20, and while I am in substantial agreement with claimant's description of how the Bacto-Unidisk is used, I must insist, as a physician and scientist, that these usages are unquestionably uses in the diagnosis, care, treatment, prevention, and mitigation of infectious disease in man."

* * * *

[116] *Redirect Examination*

By Mr. Trumbauer:

Q. Dr. Wolfe, I noticed on one of the questions that was submitted to you by counsel toward the end of his cross-examination that you emphasized to him that this information received from this sensitivity testing was for use in making your ultimate determination of treatment; is that right?

A. This is correct. And I might say that this is an ever-increasing use; that the numbers of disk sensitivity tests being performed is growing rapidly. It is already in huge proportions, but it is common usage—I think is the word I would have to use for this—rather than just in specialized medical centers or large medical centers.

* * * *

[118] The Court: Doctor, as you probably know, there are many places in our country yet where the doctor may have a small hospital with no laboratory, like Beaver Island in your own Lake Michigan, and, if he had a patient that come to his hospital with a liver condition, would the [119] publication that you and your associates have published, "Effect of Large Doses of Aureomycin on the Human Liver,"—would there be anything in that article that might assist him in the administering of aureomycin for this condition?

A. Yes, sir.

The Court: Then he could use your publication as a guideline, couldn't he?

A. As a limiting guideline.

The Court: Well, it would be a—

A. (Interposing) Because, as a result of that publication, the dosage was revised downward because this had a very bad effect.

The Court: So he would obtain information from that publication that would be helpful to him in administering to the patient that had the liver condition?

A. Yes, sir. It would be one of the many sources that he could draw on.

* * * *

[122] The Court: What are you feeding into the computer?

A. The disk sensitivity results.

The Court: Of many tests?

A. Of many tests. Thousands of tests. Each month. So that this is information that is a month old. However, we can utilize it because of the fact that if we are dealing with a particular organism that has been acquired in our hospital setting, such as a post-operative complication, we will then be able to utilize direct information on similar patients exposed to these disks before we have actually got the results from that particular patient's disk sensitivities, rather than relying on the publication from another medical center who would not have the same type of disk spectrum.

The Court: Would that mean, Doctor, since you have already told us in relation to your own particular practice that you are interested in getting an immediate diagnosis and to identify the organism, and then submit it to tests, but also, as I understand it, you do or do not on occasion give the patient an antibiotic that may or may not be changed after the results of the test,—what use would the computer be in relation to that procedure that you are talking about following?

A. It is a means of refining the rough information that you get [123] from a disk sensitivity even a little more, in this fashion—

The Court (Interposing): How would you use it? When it is completely fed in there, at least fed in to the extent you and your associates feel it is competent to function as a source of information, I presume—immediate information—what would be the results of its use? The procedure? The mechanics of its use?

A. The mechanics of its use would be that upon the isolation of an organism, and pending the results of the disk sensitivities, I could refer to the computer results in the following fashion:

Find out, for instance in the case of pneumoccoccus, that penicillin was effective fifty times more than erythro-

mycin was, and perhaps twenty-five times more effective than chloramphenicol or chlortetracycline.

It puts it on a more precise statistical basis for the antibiotic choice, since there is an area of several from which to choose. This was established.

The Court: And is it your impression that the computer will have to be certified by the Secretary? I am serious about this.

A. That had never occurred to me.

The Court: I am doing the smiling myself, but in a different way. You are getting information from a mechanized source that is the same type of information [124] that assists you, apparently, in your diagnosis of what should be done with the person under your treatment.

* * * *

[125] *Re-cross Examination*

By Mr. Williams:

Q. Dr. Wolfe, what do you feed into the computer other than the bare results or the bare information which you obtained from the sensitivity tests?

A. The things that are fed into our computer system in the programming is the origin of the specimen—this would mean the throat; the place in the hospital where this specimen was obtained or first collected, such as a nursing unit; and the actual organism identification.

Q. Now, you have identified the organism in some manner other than through the sensitivity tests?

A. That is correct. And finally the disk's spectrum.

Q. Are the—is that all you—

A. (Interposing): Those are the four categories.

Q. Do you have a computer for other tests, other information obtained from other tests?

A. Yes, sir.

Q. And what you you feed into that? Take a particular example.

A. Well, there are no other examples in the field of infectious disease, but in the field of cardiology they feed symptoms, diagnosis, capsular findings, and arrive at a

statistical analysis of a diagnosis. It is a diagnostic procedure.

Q. In any of these situations where you are using a computer [126] to get this conglomerate result, do you feed in the kind of culture media that was used?

A. That would be a matter of programming. We don't. It could be.

* * * * *

[130] DR. JOSEPH PAUL TRUANT

thereupon resumed the stand as a witness on behalf of the Libelant and, having been previously duly sworn, testified further as follows:

Direct Examination (Continued)

By Mr. Trumbauer:

Q. Dr. Truant, in your long experience in this field which [131] you testified with respect to yesterday, namely the area of sensitivity disks, have you become familiar with the fact that the Federal Government has set forth certain regulations relative to the use of antibiotic sensitivity disks?

A. Yes, I am familiar with—I believe it is—Section 147. It deals with rules and regulations regarding the certification of antibiotic disks.

Q. Now, are the disks which you purchased at Ford Hospital disks which have been certified under the provision of these regulations?

A. To the best of my knowledge. I don't check on each batch, but I am told by the company sales people that these have been pre-checked by the Food & Drug Administration, but I don't check on each batch.

Q. But, as far as you know?

A. Yes, they have been previously certified.

Q. Would you permit, or do you permit, purchase of disks which have not been so certified?

A. No, we absolutely would not get involved in this situation, because between the period of 1954 to 1960, we had many problems before certification.

Q. What do you mean by that?

A. We ran into variations due to either too large or too small a quantity of drug being incorporated in the disk. We, by comparative studies—

[132] Q. (Interposing): You are referring—we will use this Exhibit 1 as an example. You are referring to disks as this?

A. They were not Unidisks, but they were disks manufactured by both Difco and Baltimore Biological. We found a number of discrepancies in the disks during this period, and I have much more confidence now that the disks are certified by the Food and Drug Administration, and since we want the best results possible, I feel very confident in buying disks which have been certified by the Food and Drug Administration.

Q. Does this have to do with what you might call standardization of this procedure?

A. Yes, one might call this standardization—establishing uniformity of concentration in each disk.

Q. In your experience, what are some of the hazards or dangers of the use of a procedure involving sensitivity disks where the disks have not been subjected to a standardization such as set forth by the certification?

A. There is a possibility of having too low a potency in that disk—too low a concentration of chemotherapeutic agent—in which case the organism would tend to be reported out as being a resistant one, or being more resistant than if the true potency were in the disk; and, on the other hand, you might have too high a potency, which means that you would report a sensitive organism which in fact might not be in that very [133] sensitive category.

So it might be an error in either direction, which would give us false readings and we would be giving misinformation to the clinician, and he in turn, obviously, being unaware of this situation as we would be, would not treat the patient properly. Therefore, we feel that we can't take this chance of using disks that are not certified. It, to us, is a real hazard.

Q. I see.

A. And based on previous experience from the laboratory end, and discussions with clinicians, who in this period between 1954 and 1960 frequently brought up the discrepancies to us, and we would recheck them and find that frequently the disks were either too low or too high a potency, and we decided to use certified disks only.

Q. Not all drugs or chemicals are subject to certification, are they—I mean in this broad spectrum—

The Court (Interposing): What?

Mr. Trumbauer: Not all drugs or chemicals that you use are subject to certification.

The Court: We are not concerned here with drugs. We are concerned with an article, as I understand. That is what I understand this lawsuit is about.

Mr. Trumbauer: Well, I think one of the basic [134] areas that we are concerned with here, your Honor, is whether it is a drug.,

The Court: You mean that disk there?

Mr. Trumbauer: Yes.

The Court: That is what the statute speaks of as an article.

Mr. Trumbauer: Under the total definition of drugs, yes.

Q. (By Mr. Trumbauer, continuing): What I am getting at, Dr. Truant, is: Do the antibiotics have any peculiar characteristics which in your view make it more necessary that they be subject to strict manufacturing procedures?

A. Well, I certainly think in the preparation of disks, it has been well demonstrated that unless one standardizes his procedure either within the hospital community or by a manufacturing company, that unless you have good standardization, you may well produce a disk of poor quality, which would give misinformation to the laboratory worker, and, eventually, to the clinician.

Q. How does this differ, if it does differ, in your view from the information that you would obtain from a book or literature on the subject?

A. Well, there is a very real difference here that I didn't cover yesterday, and that is, that the information

that you get from [135] textbooks, though informative, is not direct information on the organism that you isolate from a patient. In other words, we use the information from textbooks as a sort of procedural guide in the laboratory, and I believe the clinician does the same thing, but I want to stress the point that each patient must be worked up from the standpoint of determining the type of organism or organisms which may be producing the disease in this individual, and to follow through and run the susceptibility pattern on that particular isolate, because we may be dealing with the same organism that is discussed in the textbook in terms of what we call species, but there are many strain differences in determining antibiotic or chemotherapeutic spectrum. In other words, one strain may be resistent, the other slightly sensitive, and still another more sensitive. Therefore, I want to emphasize that for each situation we may have a different set of criteria.

So I would emphasize that we should run susceptibility tests on the organisms isolated from that patient, even though we may have general information on the degrees of susceptibility and resistance of the general group or type of organisms isolated from that patient. As an example, if we are dealing with a staphylococcus that has been isolated from patient A and a staphylococcus isolated from patient B, both are members of what we call the same genera staphylococcus, [136] but they have completely different antibiotic spectra. So even though the book may say that 40, or 60, or 70 per cent are sensitive to penicillin, we would do much better to have absolute data on each of those organisms in order to best treat the patient.

Q. In your program at Ford, have you utilized computer techniques in the gathering of information in connection with sensitivity tests?

A. Yes, we have just completed an evaluation of three years of records which we have accumulated in our department, using the I. B. M. computer. I believe the number is 1610. I have not done this all by myself, but with the help of my staff and the staff in the computer room,

we have evaluated the number of organisms which are susceptible, were susceptible, moderately susceptible and slightly susceptible and resistant; and using all the antibiotics which are used within our laboratory. In other words, we did a sum total of all organisms isolated from the majority of the services, and we have published this data in the current Henry Ford Hospital medical bulletin.

Now the reason for performing this study is to see what the general susceptibility and resistant patterns are for the organisms in our hospital community, but I would caution you that this information from our standpoint is [137] only utilized on the basis of its establishing a trend in one direction or the other, and I have a very good example to give you here.

If we go back to the discussion of beta hemolytic streptococci, we learned yesterday that a large number of these organisms are susceptible to penicillin, and penicillin would be the drug of choice. Now, if the patient has a hypersensitivity to penicillin, the doctor would have to choose one of the other drugs. Two of the more common possibilities are tetracycline and erythromycin. We found from the data that 98 per cent of the beta hemolytic streptococci were susceptible to tetracycline and erythromycin, and through the years we thought that the majority, very large majority, were also susceptible to tetracycline, but we find 10 to 18 per cent of the beta hemolytic streptococci showing resistance to tetracycline.

Now this means to us that we are finding more and more organisms of the beta streptococci group showing resistance to tetracycline. Therefore, the doctors are being alerted that the drug, the second drug of choice here, would possibly be erythromycin rather than tetracycline. So the information that we have gained from the computer has shown us this trend, but we still must run susceptibility tests on the organisms using erythromycin because some two or [138] three per cent are resistant. So in order to be sure of our therapy, we should run the susceptibility tests. In other words, we cannot depend solely on the information obtained from the computer.

Now, this is one example. It becomes even more important if you are dealing with staphylococci or members of the gram-negative group, because here you have a very wide variation in antibiotic spectrum, and the data you get from the computer certainly just shows a trend. You must perform the antibiotic susceptibility test on these organisms.

* * * *

[140] Q. (By Mr. Trumbauer, continuing): The data that you set into the computer is based upon the information that you have gathered from the running of these tests; right?

A. From the routine testing procedure.

Q. In the final analysis, aren't you relying fundamentally on the accuracy of the information that you receive from the tests?

A. Absolutely.

Q. In order to feed it into the computer?

A. Yes.

Q. If you had the finest computer and you were feeding inaccurate information into it, based upon sensitivity disks which are not giving you accurate information, what value would the information be that you got from the computer?

A. It would be misleading.

The Court: Do you know whether or not if you fed absolutely accurate information into a computer, it isn't possible to get inaccurate information in return?

A. The problems that we have been able to observe, your Honor?

The Court: As a general proposition I am talking [141] about?

A. No, you can never be absolutely sure.

The Court: All right.

A. But we have put in our own set of controls here. We have performed the evaluation. We have two technicians who spot-check the data. We have gone through five or six procedures double checking on the machine and on the mechanics.

Mr. Trumbauer: Thank you, Doctor.

The Court: Any cross-examination?

Mr. Williams: May I make a statement preliminary to cross-examination, your Honor?

The Court: Yes.

Mr. Williams: I don't consider that the question of whether Dr. Truant or anybody else considers certification desirable to be a legitimate part of this case. It was not made a part of the original case on the motion. It came in later. It was not made a part of the original case that came in later on redirect examination. I didn't object because your Honor is sitting without a jury, but we are now placed in the position we shall have to answer this.

The Court: What does the Government say?

Mr. Trumbauer: Well, they have already gone into this area by way of affidavit, your Honor, in much greater detail than we have here. We were just trying to [142] determine from this witness—

The Court: (Interposing) Actually, I don't quite connect the testimony with any great degree of importance, for this reason: That I didn't know it was the function of the Food and Drug Administration to standardize commodities for sale, but whether it is or not isn't too important, because what Dr. Truant testified adds, in my analysis of it, to this: That he has within his own competency in his laboratory the ability to examine and test the potency of these different antibiotics, and these different articles, and he can make his own determination on whether or not the product he is examining comes within the standards the Ford Hospital has in relation to the purchase of that particular commodity, and it isn't too much different than any other commodity that is on the market. You make a determination on the basis of what you know about the product—an automobile, a fountain pen, or anything else. So he can, as his testimony indicates, conduct his examination in his own laboratory. He doesn't have to rely upon the certification. He says that he does because that probably saves him the time by accepting the certification of conducting this examination, but he can standardize the products his purchasing

department wants to buy, and, I presume, like departments in the hospital, requisition what they want the purchasing agent to buy.

[143] The Witness: Can I answer that, your Honor?

The Court: Yes, you can answer that any way you want, but it all adds up, to me, in quality control, somebody said around here, and they have that in every plant.

The Witness: Yes, we have it, but we can only check the occasional disk here and there, and it became too great a job during this early period to follow through in detail on the large number of antibiotic disks that we were using, and we have been so pleased since certification came through, because we have a very uniform product throughout all the antibiotics we examine. We have established confidence in these products based on the certification procedures.

The Court: Well, I am appraising your testimony as you gave it. Now you are enlarging upon it, and I still say it is a question of quality control, that you have within the province of your own laboratory to determine, and you have also, in my opinion, a sales problem on the part of the manufacturer. If he isn't putting out a product that isn't salable, he isn't going to be around too long.

So I think that the testimony was admissible, and all you did was make a statement anyway. You didn't make any objection to it. Don't hesitate to object because there isn't a jury. I am the jury.

[144] Mr. Williams: I understand that, your Honor, but I am perfectly willing to deal with this problem if the Government desires to deal with it.

The Court: Well, apparently they do. They have offered testimony.

Mr. Williams: I might say that the reason that we dealt with it in the affidavit referred to by counsel is that the Government brought it up. We hadn't thought it part of the case, still don't, but we are willing to make it part of the case, and I feel I must examine Dr. Truant in view of some of the statements he has made, if you will permit it.

Mr. Trumbauer: Well, I certainly have no objection to that.

What we are trying to do, your Honor, in this testimony is to differentiate and to show the—

The Court (Interposing): What you are actually trying to show, in my opinion, is that the legislation has merit.

Mr. Trumbauer: That the legislation requiring this certification has merit.

The Court: Yes.

Mr. Trumbauer: As opposed to the other examples of the use of a book, or the use of some other source of information; that because of the need for the * * * [145] standardization that this legislation, which the Court is dealing with here, actually—

The Court (interposing): I don't think anybody can dispute the fact that when you are talking about a doctor making a diagnosis of any kind, that he has to draw on many sources of information, not the least of which is the years he spent in medical school.

Mr. Trumbauer: Yes.

The Court (continuing): And medical publications that he has in his library, and special papers that you have brought out here in relation to the qualifications of your experts. All of that is information that a doctor has to draw upon, as a lawyer has to draw upon the traditions of the profession. Millions of different things, in my opinion, add up to the fact that a certain person is able, both legally and morally, to make a diagnosis of an ailment than some other person.

So we are talking about something that I don't think anybody can dispute. I don't think Dr. Truant would dispute, or Dr. Wolfe, that you have to draw upon many different sources.

Mr. Trumbauer: Many different sources. I think there is no question about that.

Mr. Williams: Your Honor, we would not dispute [146] that. The problem here right now is not whether the certification system as applied to antibiotics is desirable or necessary, but whether or not it extends to these disks.

The Court: The real problem is whether the Government is going to be able to condemn and you are going

to get this shipment back. That is the basic problem.

Mr. Williams: The shipment is our least interest, of course.

The Court: I know it is, but that is what the lawsuit is about.

Mr. Williams: Yes, sir.

The Court: That is why it is here.

Cross Examination

By Mr. Williams:

Q. Dr. Truant.

A. Yes, sir.

Q. Do you use mandelamine disks in your laboratory?

A. We do.

Q. Are they certified?

A. I cannot so state, but I might rebut all this by saying that they are not antibiotics—that is not an antibiotic.

Q. Therefore it is not certified?

[147] A. I can't answer that question.

Q. Well, are you under the impression that disks other than antibiotic disks are now being certified by the Food and Drug Administration?

A. I think you are absolutely correct, just the antibiotic disks.

Q. So you are using mandelamine disks which are not certified?

A. That is right.

Q. Do you use sulfonamide disks in your laboratory?

A. Yes.

Q. Are they certified?

A. No, they are chemotherapeutic agents.

Q. Are they certified?

A. No, they are not.

Q. Did you not state in an affidavit which was filed in connection with the proceedings for summary judgment that you would not use in your laboratory any disks which were not certified?

A. Well, I would have to qualify that, obviously, and say these would have to be antibiotic disks. We would prefer to have certified disks.

Q. You just want the antibiotic disks certified. You don't care about the others?

A. No; we have been following it up with members of the Difco Corporation, and I have discussed this many times in the past. I would like to see certification for all of the chemotherapeutic [148] agents. It would certainly be much easier on us in the laboratory.

Q. Could you think of any other drugs you would like to see certified?

A. Within this realm?

Q. There are a lot of dangerous drugs on the market which aren't certified?

A. Well, I am thinking in terms of my own problem in bacteriology. We would like certification for the chemotherapeutic agents we use in our laboratory.

Q. Dr. Truant, you stated you were concerned if there were no certification system, that a disk might bear an antibiotic which was of too high a potency, or too low a potency. How do you determine how high or how low potency should be?

A. Just based on the experiences of many people, both in the clinical and laboratory field. They have arbitrarily chosen these concentrations.

Q. What concentrations?

A. For instance, 2 and 10 for penicillin disks, for things like chloromycetin and tetracycline, 5 and 30—5 micrograms and 30 micrograms. These are about. I am not saying that these are exact amounts. These aren't magic numbers. They can vary in either direction, if this is what you are getting at. This is shown up on the basis of general experience by many [149] people. They have decided that these concentrations sort of fit in with the clinical results that they have gotten in patients.

Q. Do you always use disks of two concentrations in each test?

A. No, not always, because, for instance, with methacillin and oxycillin, two of the synthetic penicillins, only one concentration is prepared of each.

Q. Might you sometimes use a disk of two micrograms?

A. Two for penicillin?

Q. Is it two micrograms?

A. Units.

Q. Two units in the case of penicillin?

A. Yes.

Q. Might you sometimes use a disk of only two units of penicillin in concentration?

A. Instead of using the 2 and the 10?

Q. Yes.

A. Occasionally, if they happen to be out of the disks. We don't recommend it, but it is done.

Q. You have a difference there of six units between 2 and 10?

A. Eight units.

Q. Between 2 and 10?

A. Yes.

Q. That is a rather substantial variation, isn't it, and yet you [150] are satisfied to use the two?

A. No, I didn't say I was satisfied. I said I preferred using two and ten. I didn't say I was satisfied with two.

Q. But do you think you can get a good result with the two?

A. If you use Anderson's procedure and you measure zone size, and you establish zone size for a susceptible organism, and if you have performed this by testing a large number of strains and knowing what the approximate zone size should be for very sensitive organisms. Anderson and others have used this successfully. We have only compared it with a few organisms, compared this procedure, single potency disk with the two potency system, in twenty or thirty instances. So I can't answer that question. I still prefer to use the two-disk system.

Q. Do you have any specific example of a disk of a concentration which is below that you think it should be which has misled the physician to the detriment of a patient?

A. I cannot put my finger on it now, but recall that there were a number of instances brought to my attention by individuals in the infectious disease department.

Q. But, Doctor, you have talked as though this was something that might happen any time and might happen frequently, and yet you are not perpared to give us any examples?

A. I can. I don't have it available. It would have been searched [151] out. If I had time, in conjunction with the infectious disease people, I could probably find instances.

Q. Wouldn't it have been useful, if you were going to testify to that effect in this case, to have been able to support your testimony by facts?

A. Yes.

Q. Are you saying, Doctor, in your testimony, that the disk test identifies an organism?

A. No. We said that the disks are an aid in the identification of an organism. It is one of the methods which assist in the identification of organisms.

Q. What kind of background of information do you have to have in order to get this information from the disk, or some of it?

A. Let's take a specific example, such as the bacitracin disk.

Can I call on an exhibit which I brought today, a plate?

Mr. Williams: If you want to introduce it in evidence.

Mr. Trumbauer: We would first mark this as Libelant's Exhibit No. 4.

(A petri dish was marked Libelant's Exhibit No. 4 by the Reporter.)

Mr. Trumbauer: This has now been marked as Libelant's Exhibit 4. Do you want to examine it before he [152] it?

Mr. Williams: Yes, I want to look at it, but I want to be sure the bug is well hidden.

(Exhibit 4 shown to Mr. Williams.)

The Court: I was looking at the towel myself. Some years back the Government stopped supplying us with towels.

The Witness: Can I have the towel?

The Court: There is really a suspicious man.

The Witness: No, this is good aseptic technique, protecting your table. I brought this along on purpose.

Mr. Williams: Are you going to explain this exhibit, Dr. Truant?

A. Yes. Yesterday we were speaking about taking a throat specimen and subsequently using that specimen to inoculate a petri dish—the agar within the petri dish. I did not bring the primary culture with me. What I have here is a subculture of the beta hemolytic streptococcus which we suspect of being the causative agent of this patient's sore throat.

Now, in the center of this plate we have an antibiotic disk marked A, which is termed Taxos A disk. It contains bacitracin.

Q. (By Mr. Williams, continuing): Taxos A?

[153] A. Taxos A. It shows a zone of inhibition. This gives us presumative information that this may be a group of A streptococci.

Q. Why does it?

A. Why? Because Maxted & Company workers have shown, and we have followed this up, and also confirmed this fact, that 85 to 100 per cent of beta hemolytic streptococci, which are susceptible to this bacitracin disk fall into group A.

Q. So it isn't the disk that identifies the organism?

A. No, assists.

Q. It is the background of information you have?

A. Assists, but it is a piece of information that is gained very readly without having to go through the typing procedure.

See the zone of inhibition here (indicating)? Some are larger.

Q. Now, do you know the procedure which was followed in order to come to this conclusion that you just stated with respect to the beta hemolytic streptococcus?

A. Do I know the procedure?

Q. Yes.

A. How do you mean?

Q. You said you knew from information available to you from other sources?

A. Yes, and from our own experience.

[154] Q. And from your own experience?

A. Yes.

Q. That, I believe you said, 90 per cent of the beta hemolytic streptococci strains were susceptible to Taxos A?

A. Yes, 85 to 100 per cent.

Q. What procedure did you go through to get this information?

A. We isolated a number of beta streptococci, some four or five hundred. We did the typings on these. We performed the Lansfield typing procedures, and we also performed the disk tests, bacitracin disk tests, on all of these strains.

Q. And you found—

A. (Interposing): We found that some 85 per cent were susceptible.

Q. You found that organism, the identity of which you knew, was resistant?

A. No, we didn't know the identity. When we first started, we did not know the identity.

Q. But you found the identity of it?

A. Yes.

Q. Then when you tested it here, you found its resistance. Therefore, in the future, you would know when you got this resistance you might have this beta hemolytic streptococcus?

A. When we got the susceptibility, not the resistance.

Q. I am sorry. The susceptibility.

A. Right.

[155] Q. You refer to absolute data. Do you recall the context in which you used that term "absolute data"?

A. No.

Q. Well, I understood that you used it in the context of your discussion of disk test. Are you contending that the disk test gives you absolute data?

A. I don't recall. Can you read the statement again? I mean, you say—

Q. (Interposing): My note indicates that you got the impression across to me that the data you obtained from the disks was absolute data, but we will drop that.

A. All right.

The Court: Was that in relation to the feeding in of the information to the computer?

Mr. Williams: Could have been, your Honor. I am sorry my note is so insufficient for the purpose I am trying to use it. I believe it was that.

The Court: I think the question might have been by Mr. Trumbauer. Do you recall?

Mr. Trumbauer: I don't recall him using the word "absolute data."

The Witness: I don't recall. It is just a dangerous term to use.

Q. (By Mr. Williams, continuing): Do you happen to know—did [156] you—that Taxos A is not certified disk?

A. Taxos A? No.

Q. But you are relying on it?

A. Yes.

Q. Now, with respect to the computer, what do you introduce into the computer?

A. What we do is we first record the antibiotic spectrum for each organism that we isolate. We take this information from our log book, and we summarize the number of organisms which are susceptible to chloramphenicol, penicillin and all the antibiotics. We characterize them according to very susceptible, moderately susceptible, slightly susceptible and resistant, and the computer gives us the total number in each group.

We feed, for instance, weekly and monthly data and get the yearly figures for each one.

Q. Do you feed patients' responses into the computer?

A. No.

Q. You don't assemble that data?

A. No.

Q. In other words, you don't feed into the computer what the particular antibiotic involved in the disk test

which is fed into the computer actually does to the patient?

A. No.

[157] Q. Do you feed the kind of agar you use in the test into the computer?

A. No. The type of agar is standard throughout for each of the tests. For instance, the antibiotic testing procedures were all done on sheep's blood agar media. This is standardized, one type of media.

Q. As far as this computer use is concerned?

A. Yes.

Q. Do you feed into the computer the time it took to obtain a zone of inhibition?

A. No. This is usually in 98 per cent of the cases standardized. They are all 18 hour results, overnight results.

Q. Do you feed the width of the zone into the computer?

A. No, we don't.

Q. Do you feed the concentration of the inoculum used, or the bacteria in the inoculum?

The inoculum procedures, except for the variation between one technologist and the other, are reasonably well standardized. In other words, they all use the same procedure, but the inoculum size does vary usually between ten to six thousand, or ten to eleven thousand per milliliter. We prefer to use a concentration from ten to the sixth, or tenth to the ninth, but from our plate counts, we know this is not always true, that the range of an inoculum size is somewhere between ten [158] to the sixth, and ten to the ninth per milliliter.

Q. You say that wouldn't make any difference in the final result?

A. No, I didn't say it wouldn't make any difference.

Q. Why don't you feed it in?

A. Why don't we feed it in? Because we don't make plate counts on each procedure. In other words, with this range of counts, we are interested in the antibiotic spectrum. There may be some differences.

Q. Again, we are in this field where you are indicating that the result of the test is by no means absolute, because you have a wide variation?

A. Yes, I agree with you, sir.

Q. Did I understand you to say that the information from the computer establishes only a trend for you to consider in determining the sensitivity of certain organisms?

A. In some cases it may not even establish a trend. It may be status quo. In other words, in 1963 we may find 60 per cent of the staphylococcus strains were resistant, and the figure would be the same for '64 and '65.

Q. In other words, it is just another one of the sources of information his Honor was talking about and we talked about yesterday?

A. Yes.

Q. You, of course, wouldn't say that the computer is an anti- [159] biotic, would you? You wouldn't say the computer is an antibiotic?

A. No more than I would say a book is an antibiotic.

Q. Would you say it is used in diagnosis of disease?

A. Computer used in diagnosis? Not directly.

Q. Well, is it at all?

A. Not in our application.

Q. Now, Doctor, isn't it fair to say that on the basis of all we have heard from you yesterday and today, that the information gained from the sensitivity test is whether the organism is resistant or is not resistant to a particular antibiotic used in the test?

A. Yes, generally speaking this is true.

Mr. Williams: That is all I have, your Honor.

The Court: Any redirect, Mr. Trumbauer?

Re-direct Examination

By Mr. Trumbauer:

Q. You answered yes to Mr. Williams' last question: The basic function of this test is to determine whether a given specimen is resistant or not resistant?

A. Is either sensitive or resistant.

Q. To the—

A. (Interposing): To the antibiotic, yes, yes, having previously [160] discussed the fact that this is a qualitative test and we can have moderate susceptibility and slight susceptibility. He was obviously aware of this.

Q. But does it stop there? Isn't it true that you go further with that information and utilize it in connection with the determination of what treatment to use with respect to the patient?

A. Then I forward his information to the clinician, and then he utilizes the information in the treatment of the patient.

Mr. Williams: Your Honor, he is trying to lead Dr. Truant into an answer which is contrary to the last one he gave me.

The Court: Apparently puts you in pretty good shape.

Q. (By Mr. Trumbauer, continuing): What I am trying to get at is whether or not your answer to counsel's question encompasses all of the picture, or just part of it?

A. Can you give me an example?

Q. He didn't ask you in that question whether it is used, this information is used, in connection with the treatment of the patient, and that is what I am trying to clarify with you?

A. Well, the information once gained is forwarded to the clinician; and by the information, I am speaking of the susceptibility pattern which is obtained on that particular organism. That [161] is sent in on a report to the clinician, and then he evaluates whether he is going to use one antibiotic or the other, depending upon his clinical impressions. In other words, follow up as Dr. Wolfe discussed yesterday.

Mr. Trumbauer: Thank you.

Mr. Williams: No further questions.

The Court: Doctor, the results of the susceptibility test is not an absolute diagnosis then?

A. No, I wouldn't say so.

The Court: If it would, it would seem to me—

A. (Interposing): The isolation of the organism can, might be, an absolute diagnosis. In other words, if all

the clinical entities fit the scheme, the isolation of an organism may well confirm the clinician's diagnosis.

The Court: Have you ever had an occasion when the test disputes the diagnosis of a doctor?

A. Yes.

The Court: Is that quite a common occurrence?

A. Well, by "common"—

The Court (interposing): Does it happen quite often?

A. It happens quite frequently.

The Court: I think you said you had 500 of the susceptibility tests a day or week?

A. No, this is per month, but these are based on the organism. [162] This is not counting the individual disks. In other words, we run eight to twelve thousand disks or more per month.

The Court: Well, on occasion, as you have indicated, the test does dispute the diagnosis of the doctor in relation to the type of organism. What happens in that case?

A. Well, then they take a second specimen, or a third specimen.

The Court: Who does?

A. The doctor does.

The Court: And sends that back to the laboratory?

A. To the laboratory?

The Court: So that would seem to indicate that he feels that he is sure, but he isn't sure of the result of the susceptibility tests that were made by the disks?

A. No, he frequently wants to confirm this finding. This is done with blood counts as well.

The Court: No, I am just talking about any kind of culture. Well, the one you used taken from the throat of a person who was suspected of having a streptococcus throat infection. If the doctor calls upon two more tests, susceptibility tests, then, if, as you say, he wants to confirm, then he isn't sure.

A. Well, throughout these proceedings I have noticed we have conveyed the wrong impression by using certain examples. [163] Now, if I might qualify this in terms of throat cultures, these are not frequently repeated, but in terms of blood cultures, they are. In other words, where

it is a more serious situation, the doctor frequently goes back and takes another specimen. If there is any question in his mind, he repeats it. So that the repetition of the procedure in the selected instances doesn't account for the majority of cases. So I might have misled you in this situation.

The Court: What I have to do is determine this matter from the evidence and exhibits. That is why testimony is important to my function.

A. Yes, sir.

The Court: Well, if the result of the susceptibility test would be an absolute diagnosis, then all that would be needed, would it not be, would be to put it on the chart that this patient should have penicillin at a certain time, and the nurse would administer it, but it isn't done that way, is it?

A. The doctor?

The Court: I don't mean the doctor.

A. No, it can't be evaluated by the nurse. The doctor has to evaluate it and then put the orders on the chart.

The Court: And then the nurse administers it?

A. And the nurse administers it.

[164] The Court: That is all I have.

Mr. Williams: May I inquire?

The Court: Yes.

Re-cross Examination

By Mr. Williams:

Q. I wonder, Dr. Truant, if we could clarify this situation by distinguishing between two tests. We have been talking about two types of tests. One, the sensitivity test, using the disk; and the other is the test by which you identify the organism or the bacteria in the isolate, or swab from the human being. Isn't that correct?

A. Yes; in terms of using disks or all other methods?

Q. No, just in terms—we are talking about two different things, and I am not sure but what we have confused matters. One is the test resulting in identification of the bacteria, whatever it may be, in the organism, in the swab or isolate?

A. Specimen.

Q. Specimen? Good; and the other is the sensitivity test, susceptibility test?

A. On the organism.

Q. On the organism. The first one has to do with identification and is related to diagnosis. That is clear, isn't it?

A. Very clear.

[165] Q. The second one, having to do with susceptibility, is a source of information used by the physician?

A. Relating to treatment and cure.

Q. Relating to treatment. As a guide line to treatment; is that right?

A. Yes, absolutely.

The Court: Anything further, gentlemen?

Re-direct Examination

By Mr. Trumbauer:

Q. Doctor, in your experience with regard to the word "use" of a procedure, such as, for example, the susceptibility test, or any of the other tests that you may run, is it your understanding from the standpoint of your professional competence, that the word "use" is restricted merely to a procedure which gives an absolute result, final result, a result which is not taken into consideration with other factors?

A. That is hard to follow.

The Court: Yes, it is. It is a hard one to answer, because you are getting into the area of guessing a diagnosis. I don't think you are going to get anybody to admit that is the way they make a diagnosis.

Mr. Trumbauer: I am trying to get what you understand by the word "use."

[166] Your Honor, the Court inquired if this was an absolute—

The Court (interposing): Diagnosis.

Mr. Trumbauer (continuing): —test, diagnosis.

Q. (By Trumbauer, continuing): Now, does a procedure have to be an absolute diagnosis for you to consider that you are using—this is being used, for example, as an aid in the treatment of disease?

A. As you know, it is usually not an absolute diagnosis. It is suggestive, strongly suggestive, but when you say "absolute," this is the point that Mr. Williams was getting at. I would not use this term "absolute."

Q. With regard to the word "use"; is that correct?

A. Yes. Now, I find this hard to answer, because I just can't pinpoint. Can you give me a specific example?

Q. Well, you have stated that the disk test is used, results obtained from the disk test is used, in your judgment, as a guide line in the treatment of disease?

A. Yes.

Q. In order for it to be used, as you understand the word "used," must it be the only thing that the physician relies upon?

A. No, no. He relies on other information, not only this particular bit of information.

Q. But in spite of that, do you still feel that the disk is being [167] used as an aid in the prevention of disease or treatment of disease?

A. Certainly it is being used.

Mr. Williams: May I?

The Court: Yes.

Re-cross Examination

By Mr. Williams:

Q. Have you now changed your testimony, Dr. Truant?

A. No, I don't think I have.

Q. You have testified yesterday and today.

The Court: He is trying to diagnose your testimony.

Q. (By Mr. Williams, continuing): You have testified consistently yesterday and today that the disk test, the information obtained from the disk test, is a guide line to treatment?

A. Yes; and this is what Mr. Trumbauer was referring to.

Q. Is that what you understood him to say?

A. Yes, that the information that we give is used by the clinician.

Isn't this what you were getting at?

Q. May I finish, please?

My understanding of Mr. Trumbauers' question was that he was attempting to equate the use of the disk to the [168] use of the information obtained from the disk test, a test which employs not only the disk but also a petri dish, an agar isolate from a culture, which consists of an isolate and I don't know what else is in a culture, but you have got all of those things involved in the disk test from which you get information. He is asking you to isolate the disk from this whole test procedure and say that it is used in diagnosis.

Mr. Trumbauer: Your Honor, counsel is getting into argument and I feel obliged to answer.

This is not what I asked this man.

The Court: I know what you asked. What you actually wanted from the witness, if you get it, is testimony that completely locks the test in with the provisions of the statute. That is what you are asking for, and, of course, I have been around long enough to know what you are asking for.

Mr. Trumbauer: I think this is really part—

The Court (interposing): You are just taking the words out of the statute and you want it to be corroborated by the witness. I don't blame you if you can get away with it, but I know what you are doing.

Mr. Trumbauer: I wasn't trying to hide it.

The Court: You couldn't unless you used deaf [169] dumb language.

Mr. Trumbauer: I think we have agreed throughout the case that the experts could help the court.

The Court: Yes, and I appreciate the help I am getting.

Mr. Trumbauer: In understanding of what this term "drug" means, and that is what I was trying to get at, and it seemed to me through the course of the questioning the Court had asked several times whether this test was the final absolute test; and I was merely trying to develop from the witness whether his understanding of the word "use" encompassed procedures which were not necessarily the only thing—that the information gained

from it was the only thing the physician was using in his final treatment.

The Witness: No. We discussed he uses other information. He takes this bit of information along with his physical and other findings.

The Court: All I was trying to do by my question was to establish on the record the fact that somewhere and some time in relation to what we have here, some human being with a medical degree has to make a diagnosis; and that is made, apparently, as we know, after a certain amount of investigation from one or many sources.

Mr. Trumbauer: Yes.

[170] The Court: I don't think anyone can disagree with that.

Any further questions?

I guess that is all, Doctor. Want to take Exhibit 4 along with you?

Do you want that kept here?

Mr. Trumbauer: I should move for the introduction of this, since we have marked it.

The Court: I have already got it admitted. I don't think you have any objections.

The Witness: It should be sterilized.

The Court: You can have it then. Our sterilization process isn't any better than our cold storage there on the right.

You don't want that exhibit?

Mr. Williams: No, as a matter of fact it is an uncertified antibiotic. I don't know what point it has in the record anyway.

The Court: Gave us a chance to go into that.

(The witness was excused.)

The Court: You said you had some witnesses this morning?

Mr. Williams: Yes, sir. Do you want to have a recess before we go into that?

[171] The Court: Yes, I would like to have one, but we have a regular time for taking recesses, and I usually make appointments when I am in trial. So, I have got a

couple of lawyers coming over here a little bit later. If I take a recess now, I will miss them.

Mr. Williams: All right, your Honor. I will ask Dr. Keefer to come forward.

DR. CHESTER SCOTT KEEFER was thereupon called as a witness by the Claimant, and after being duly sworn, testified as follows:

Direct Examination

By Mr. Williams:

Q. Doctor, will you state your name for the record please?

A. I am Chester Scott Keefer.

Q. Will you state your address, please, Dr. Keefer?

A. My address is Boston University School of Medicine, 80 East Concord Street, Boston, Massachusetts.

Q. Dr. Keefer, what is your present occupation and position?

A. My present occupation? I am professor of medicine emeritus and consultant in medicine to the University Hospital of Boston University. I am also consultant to the dean of the Medical School at the present time on matters dealing with medical [172] education.

Q. Can you give us some of the former positions in medicine which you have held?

A. Well, I graduated from Johns Hopkins University School of Medicine in 1922; remained on the staff for four years; and then I had been a member of the medical staff of the University of Peiping Union Medical College in Peiping, China, Harvard Medical School, Boston University.

Q. Have you taught medicine?

A. I have taugh medicine, sir, for forty-four years, ever since I graduated from the medical school.

Q. Have you done medical research?

A. I have always done medical research throughout my medical lifetime.

Q. In what particular field, if any?

A. I have concentrated mainly in the field of infectious diseases for the last forty years, and during the past thirty years I have been intensely interested in all antibacterial agents, which includes the sulfonamides and all the antibiotics.

Q. Have you written any publications on these subjects?

A. Yes, I have written numerous papers on the action of a variety of antibiotics and other microbial agents.

Q. Have you written books on those subjects, Dr. Keefer?

A. Yes, we published one, a monograph on penicillin, summarizing [173] 10,000 cases that were studied by the profession in the United States; another monograph on streptomycin, 3,000 patients studied by physicians in the United States and abroad.

Q. Have you held research positions in hospitals?

A. I have been the Director of the Robert Dawson Evans Department of Clinical Research and Preventive Medicine of Massachusetts Memorial Hospital for twenty years, and supervised the work that was done in the infectious disease unit, which consisted of the unit of the Haines-Memorial, which was our infectious disease unit, a hospital of 200 beds, as well as the infectious disease unit in the general hospital.

Q. What was the first antibiotic developed, Dr. Keefer?

A. The first antibiotic developed was gramicidin, which is now known—which was a combination of two antibiotics know as tyrothricin and tyrocidine.

Q. What was the next antibiotic?

A. The next antibiotic was penicillin.

Q. Then thereafter?

A. Then streptomycin, bacitracin, tetracyclines, and since then there have been a large number. At the present time there are at least twenty to twenty-five antibiotics available for use by the physician.

Q. When was penicillin first developed so that it was usable in clinical work?

[174] A. Approximately 1939 in Great Britain. In the United States in 1940.

Q. Was that about the time of the Second World War?

A. Yes, sir.

Q. Did you have a function in connection with the use and disposition of the available penicillin at that time?

A. Yes, sir. I was the Chairman of the Committee on Chemotherapeutics and Other Agents of the National Research Council, and we were requested by industry and by the Committee on Medical Research of the Office of Scientific Research and Development to study penicillin, collect information from doctors, so that this information would be available to the Armed Forces for the treatment of infections which were common and prevalent in soldiers and sailors, and were allotted a certain amount of penicillin every month by the War Production Board after the order was issued placing penicillin under allocation.

Q. Was this a presidential order?

A. This was an order from the War Production Board.

Q. I see.

A. Once we received this allocation, physicians who had patients with infections that we were studying, such as wound infections caused by the staphylococcus, pneumonia caused by a variety of organisms, penicillin was forwarded to him, the physician, [175] and he in return sent us a report. Once these reports were collected, analyzed and studied, the information was passed on to the Armed Forces and was also published in medical journals and in this monograph which I referred to.

Q. Did you have occasion to analyze the reports made on the penicillin which was distributed by you?

A. Yes, sir. We had this 10,000 patients results—the study of 10,000 patients which were reported to us. We studied the records and analyzed them, added our own experience to this, and published it.

Q. When did streptomycin come along?

A. Streptomycin was introduced in the mid-40's.

Q. Did you have a similar function in connection with streptomycin to that which you described on penicillin?

A. Yes, sir. Our committee had the responsibility for organizing, planning and allocating the streptomycin which was assigned to me as the Chairman.

Q. Dr. Keefer, have you had personal experience with the use of methods of assaying antimicrobial agents and antibiotics in tissue fluids?

A. Yes, sir, from the very beginning of the study of penicillin.

Q. And what methods did you use in that work?

A. We first used, as I remember, the tube dilution method, in which a known amount of the antibiotic was placed in the tube [176] diluted serially, so as to determine the action of various dilutions of penicillin or streptomycin on various organisms.

Q. Or other antibiotics?

A. Or other antibiotics later.

Q. Now that we have so many.

A. Yes.

Q. You said—did you call it a serial dilution?

A. Serial dilution.

Q. Does that mean you have several tubes?

A. Have a number of tubes. You start with, say, one to two dilution, one to four, one to eight, one to sixteen.

Q. By one to two, one to three, and one to four, you mean concentration?

A. Yes, sir.

Q. Concentration of one of the—

A. (Interposing): Antibiotics for the organism..

Q. One of the antibiotics for the organism?

A. You can dilute both the organism as well as the antibiotic, in order to determine how many organisms are inoculated in a tube, just as you determine how many organisms are inoculated into a plate. You take a tenth of a cc. of culture, put that into a plate, incubate it for a period of 18 hours, and count the total amount of colonies on that plate. That gives you the number of organisms present.

[177] Q. You are talking about the plate test then?

A. That is the plate test, yes. That is counting the number of organisms. That is how you determine the number of organisms in, say, a tenth of a cc., or what was referred to as a dilution to the minus six, seven or nine by Dr. Truant.

Q. Getting back to the tube dilution test, the purpose of that is to determine the sensitivity of the organisms to certain chemotherapeutic agents or antibiotics?

A. That is one method, sir.

Q. And you have a jump from one part to two parts, to four parts, and so on?

A. Yes, sir.

Q. And that difference in concentration of the material in the tube, what significance does that have in connection with the validity of the test? How is that used in reading the sensitivity or lack of sensitivity of the organism?

A. Well, it is a quantitative test. If you start with that initial dilution of one unit, then dilute this out to a thousandth of a unit, you can tell whether a standard organism is killed by thousandths of a unit or by a tenth of a unit, or in between. It is much more quantitative method.

Q. Now, have you also done the disk test in your laboratory?

A. Yes, we use the disk test as a qualitative test in the laboratory for determining sensitivity, but it is not a [178] quantitative test.

Q. How long did you have this laboratory under your supervision?

A. Twenty years.

Q. Of course, you didn't do the disk test during all of that time, because the disk test is too young?

A. That is correct, sir.

Q. Now, you say that the tube dilution test is a quantitative test, and I believe you said, did you not, that the disk test is a qualitative test?

A. Yes, sir.

Q. What is the significance of that difference in terms of the reliability or accuracy of the disk test as against the tube dilution test?

A. The tube dilution test gives you more precise information and is useful particularly if you are making careful studies of patients for the purposes of research, determining how much is absorbed into the blood, what the concentration is in the blood, what it is in the urine, so

that the tube dilution test is used to determine what we commonly call plasma concentration of antibiotics or even of the sulfonamide.

Q. Are there other tests used to determine the sensitivity or resistance of organisms to antibiotics?

A. Yes, there is the cup dilution test which was used very early and may be used in many laboratories even today.

[179] Q. Is that the same as the agar plate test?

A. That is one other name for it, in which you put a small cup, glass cylindrical cup, into agar plates and fill these cups with varying dilutions of the antibiotics.

The Court: We will take a short recess at this time.

(A short recess was taken.)

Mr. Williams: I should like to have this statement of Dr. Keefer's background and qualifications identified as Claimant's Exhibit No. 1.

The Court: We go along in order. That will be 5.

(A statement of Dr. Keefer's background and qualifications was marked Claimant's Exhibit No. 5 by the Reporter.)

The Court: Any objection?

Mr. Trumbauer: No objection.

The Court: It is admitted.

All right.

Mr. Williams: May I ask the Court Reporter to read the answer to the last question?

(The answer was read by the Reporter.)

Q. (By Mr. Williams, continuing): By the use of this test, Dr. Keefer, how does one determine the sensitivity of or resistance [180] of an antibiotic—of an organism to an antibiotic?

A. It depends on whether or not there is a zone of inhibition around the cup or not whether it is resistant or sensitive.

Q. Is the cup even with the surface of the agar?

A. Yes.

Q. The antibiotic actually comes in contact with the organism?

A. Yes, it diffuses into the agar.

Q. In that respect it was similar to the disks?

A. Yes, sir.

Q. Which of the three tests we have discussed—the tube dilution, the disk and the agar plate—would you consider the least reliable?

The Court: The least what?

Mr. Williams: The least reliable.

A. Reliable in what sense, if I may ask the question?

Q. (By Mr. Williams, continuing): In the sense of determining whether a given organism is susceptible or is resistant to an antibiotic.

A. I think all three methods are useful in this connection:

A more precise quantitative method is the tube dilution method. That is the most sensitive method.

I would say the least sensitive method quantitatively is the disk test.

Q. Now, Doctor, if I may, I would like to return to the matter [181] of the Committee on Chemotherapeutics and Other Agents to which you referred earlier. When did that committee cease functioning?

A. In 1945.

Q. Why did it cease functioning?

A. Well, at that time the pharmaceutical industry produced a sufficient amount of penicillin and streptomycin so that it was made available through the usual marketing practices on prescriptions in the United States. Prior to that time, the total production of penicillin was in short supply because the demands of the Army and the Armed Forces had first call on all penicillin. We were allocated materials for investigation purposes.

Q. Do you recall the circumstances of the inception of the Food and Drug certification system?

A. Yes, I recall it quite well.

Q. Can you tell us just what happened which led to the certification system? I am not talking about any statutory definition, or any concern with the statute whatsoever. I am just talking about the need for, or the apparent need for, the certification system.

A. Well, at the beginning of the research and development on production of penicillin in the United States, the article of manufacture was very little understood, and it was extremely [182] difficult to produce enough penicillin by the methods that were available then to treat any considerable number of patients. The mold that was available had very low capacity for producing penicillin. The penicillin was produced by growing the mold in a proper medium so that new strains of Penicillum had to be discovered, new media had to be developed so that you would get a higher yield. New methods of extraction had to be developed so that you would get a higher proportion of the active material from, say, a liter of the broth, and then it had to be assayed so that you could tell how much penicillin was in a cc. Then this had to be dried into a powder, so that you would have a quantity that you could manage and use conveniently.

Now, the powder that was obtained from this process was an amorphous substance—that is, it contained more than one penicillin. It contained four that we later identified, and it contained a lot of inert substances.

So that at the beginning you were able to get a yield of about two units from a milliliter, whereas by the time it was available for general use, the yield was at least a thousand to fifteen hundred units per milliliter.

So that this was a development which was a cooperative undertaking on the part of the Government and industry and was a remarkable achievement.

[183] Q. By this you mean—

A. (Interposing): Producing penicillin that was of higher potency. When the N.D.A.—that is the new drug application—for penicillin was made effective by the Food and Drug Administration, you had an amorphous substance that had been approved to be safe as well as highly effective in certain infections that were being studied, but the total volume of the powder varied from one manufacturer to another because of the difference in the potency. So it was felt desirable on the part of the manufacturers to set up some standards and to have these standards approved among themselves and approved by

the Food and Drug Administration; and methods of assay had to be worked out so that the inventors, the manufacturers, had to teach the people in the Food and Drug Administration, their technicians and scientists, how to assay this so that there would be the same cooperative effort in order to get a standardized product. So that if you had on the label 5000 units of an amorphous substance, it might contain a tenth of a gram in one tube from one manufacturer, two-tenths of a gram in a tube from another manufacturer, you'd know there were 5,000 units in both.

Q. Did these problems lead to the certification system?

A. These problems led to the certification, yes, sir.

Q. Did you have similar problems with streptomycin?

[184] A. The problems of streptomycin were similar but not nearly so great, because a purer product had been produced before it went under clinical investigation. The chemists knew much more about streptomycin than they did about penicillin at the beginning.

Q. After streptomycin and penicillin were brought under certification, from year to year several other antibiotics were brought under certification?

A. Yes, sir.

Q. Do you recall what they were?

A. Well, the tetracyclines were brought under specification. The first was aureomycin and then terramycin; the basic formula in aureomycin and terramycin was tetracycline, but the names "aureomycin" and "terramycin" were given to this before they knew what the basic formula was. The basic formula was tetracycline.

Q. Did you have the same problems which you described with respect to penicillin?

A. No, I wouldn't say so, because this was a much purer product.

Chloramphenicol before it was introduced could be made synthetically.

The Court: Are you talking about aureomycin now?

Mr. Williams: I was talking about those which [185] were added to the statute after penicillin, namely streptomycin, chloramphenicol, chlortetracycline and bacitracin.

Then, your Honor, in 1962, the rest of those for use by man were added.

Q. (By Mr. Williams, continuing): Do you have any experience upon which you could base an opinion as to why those others than streptomycin and penicillin were added to the list of those which are certifiable?

A. I haven't any opinion. It is my impression that the manufacturers requested that these antibiotics be certified.

Q. Do you have any experience upon which you would care to base an opinion as to whether these problems exist today which formerly justified certification system?

A. I don't believe so, from my own experience and observation.

Q. You don't have an opinion on it?

A. Don't have an opinion, but I have seen no evidence that it is really necessary to certify all antibiotics.

Mr. Trumbauer: Your Honor, I would like to object to the answer that was given.

The Court: I will sustain the objection. What difference does it make? It is on the books. Might be a good statement to make to Congress, maybe.

Q. (By Mr. Williams, continuing): Doctor, as a physician, how would you classify a sensitivity disk?

A. A sensitivity disk is a laboratory article, laboratory agent, [186] that is used in the laboratory to test the sensitivity of a given organism, a known organism.

Q. To what extent, if any, is the laboratory test a reliable guide to the action of the antibiotic in the body—that is, the sensitivity test?

A. Well, it is one guide that may be used.

Q. What factors would you say would affect it which would cause a different degree of activity in the body than that found in the petri dish in the laboratory, if there are such factors?

A. This would depend entirely upon the type of infection, its location, whether or not there were abscesses present where the antibiotic could not penetrate the abscess, or whether the products of inflammation would inactivate the antibiotic; also, such complicating factors as

urinary infection, the presence of stones or some obstruction in the urinary tract.

The Court: Well, let's take that example, Doctor. How would you go about getting a sample?

A. A sample of urine for testing?

The Court: Supposing you wanted some of the flesh. Let's take anything under the skin that might be infectious.

A. Well, under those circumstances, your Honor, usually an abscess is drained by the surgeon, or it may be punctured by a needle and syringe so you aspirate some pus, and then you [186a] may transfer that to a test tube, or an agar plate, identify the organism, and then test it for sensitivity.

The Court: What I am thinking about is this: Say possibly cancer of the liver, wouldn't you have to get in there with a knife, and a surgeon clip off a piece of liver to have it tested?

A. You might, sir, and you might do what is known today as a needle biopsy, in which you insert a large needle and remove a piece of liver, and, hopefully, if the patient has cancer, remove some tissue for diagnosis.

The Court: What I am trying to determine here and get some light thrown on is the articles intended for use in diagnosis; and if it would be necessary that you use that syringe to get a biopsy, or cut open the person and clip out a part of the liver, or whatever other part was thought to be diseased—I am trying to distinguish what kind of articles were intended for use in the diagnosis—you would be using the knife, or the syringe, in assisting in relation to a diagnosis. Would you or wouldn't you?

A. Yes, sir, you would.

The Court: That is one of the problems that I have in reading the statute. I am seriously concerned about just where this article—the term "article"—has application, [187] and where it doesn't. There are so many things that may have to be used in relation to diagnosis of a human being. I don't know. That is one of my problems and I am trying to get some help on it.

Q. (By Mr. Williams, continuing): Doctor, in that regard, how would you define "diagnosis"?

A. Diagnosis is the recognition of disease or illness. That is the general medical term or interpretation of the term—recognition, identification of illness—and this may be an anatomical diagnosis, which means making a diagnosis of change from normal structure; and to use the example of your Honor, to get a bit of tissue from the liver that may contain cancer, that is an anatomical diagnosis.

Now, a functional diagnosis may mean change in function of an organ without being able to detect changes in structure. For example, if a man has Bright's disease and has blood and what we call casts and albumen in the urine, this is due to change in the function of the kidney. The kidney leaks blood and leaks albumen, and it forms casts.

There is one other form of diagnosis and that is etiological diagnosis—that is a causative diagnosis.

So physicians attempt to make as broad a diagnosis as possible in every patient, to help the patient and guide him in therapy. A patient who has heart disease, for example, [188] one often says: This is an anatomical diagnosis of mitral stenosis, functional diagnosis is congestive heart failure, an etiological diagnosis is rheumatic fever. So this is a broad designation of classification.

Q. If you look at our disk problem specifically, are you in a position to recognize the illness or diagnosis, as you say, unless you have identified the organism which you think is involved?

A. No, sir. The disk does not enable one to identify an organism.

Q. You referred earlier to taking a specimen, identifying it, and then determining by the disk method whether the organism was sensitive or resistant to a particular chemotherapeutic agent or antibiotic. Did you mean that there was one process involved there or two processes: One of identification and one of sensitivity test??

The first step is one of identification. That is the isolation of the organism; and its identification—beta hemolytic streptococcus or staphylococcus.

Q. If you skip that step, Doctor, and went right to the disk test, could you make a diagnosis?

A. Could not make a diagnosis.

Q. Dr. Keefer, what is the significance of the width of the zone of inhibition which you find around the disk which is susceptible to the particular antibiotic being tested against it?

[189] A. Well, I don't believe it has any fundamental practical significance. What it means is that the organism is sensitive, if you get any zone, and that the antibiotic in the disk has diffused in the media.

Q. Do you mean that the zone is a function of the diffusion of the antibiotic?

A. Yes.

Q. Did you hear Dr. Truant testify this morning?

A. Yes, I did.

Q. Did you hear him say that there was a method based on information accumulated by Dr. Anderson—I believe he said—by which you could read this zone on the basis of its width, and that the width meant something in the context of this spectrograph information?

A. Yes, I did.

Q. Are you familiar with that?

A. Yes, I am familiar with it.

Q. Do you subscribe to that theory?

A. I don't think this is universally accepted. This is a quantitative test—that is, the width of the zone is a quantitative measure of the sensitivity of the organism.

Q. Did you say that you thought that the acceptance of the width as a quantitative matter was not universally acceptable?

A. Yes.

[190] Q. Do you accept it?

A. No, I do not accept it.

Q. Is it your opinion that that theory is generally accepted?

A. I don't believe it is generally accepted, not even by the Food and Drug Administration—no zone interpretation of the activity of the disk contents.

Q. Doctor, if a patient comes to a physician with a condition which he believes to be infectious disease of some sort, would he ordinarily have available a choice of antibiotic drugs for that condition or just one?

A. Well, if the doctor recognized it as a bacterial infection, he has a battery of antibiotics he might use.

Q. Are antibiotics effective against anything but bacterial infections?

A. Some antibiotics are effective against fungal infections, but no antibiotic is effective against any virone infection.

Q. It is sound to say—I believe you have answered that. I will withdraw that.

Does the test or the result of the information obtained from the sensitivity test indicate a concentration or the amount of the inhibiting substance, the antibiotic in our case, which should be used on the patient?

A. No, sir, it does not.

Q. Would you say, then, that the disk is used by the physician in [191] the diagnosis of a disease?

A. No, sir, it is not used in the diagnosis of disease.

Q. Is it used in the treatment of disease?

A. It is used as a guide line in some cases for the treatment of disease, particularly a selection of an antibiotic.

Q. Is it the disk or the information obtained from the test?

A. It is the information obtained from the test.

Q. How about the prevention of disease? Is the information obtained from the test ever used in the prevention of disease?

A. No, sir.

Q. Could you just briefly give us some of the other sources of information which might be used by the physician in diagnosis?

A. The diagnosis of an infection, as an example?

Q. Yes, that is right.

A. Well, usually in the diagnosis of infection, the patient complains of not feeling well. He may start out with a chill. Then he develops fever, and he feels hot and

chilly. He may sweat. He may ache all over. He may have pain in the back. Usually these are the general constitutional symptoms of infection.

Then the doctor always asks questions concerning localizing symptoms or signs of an infection, such as a sore throat, a severe sore throat, difficulty in swallowing.

Then there is the examination of the patient, [192] physical examination of the patient. If it is a sore throat, he looks for a rash which may be scarlet fever. Scarlet fever can ensue due to streptococcal infection.

From that information alone, an experienced physician knows that the chances are 99.9 per cent that the patient has a beta hemolytic streptococcal infection of the lymphoid tissue of the throat involving the tonsils and the adenoids.

Q. What would he then do?

A. He would then promptly give penicillin in adequate doses, and continue it for a period of seven to nine days. He might or he might not take a culture. If he took a culture, the culture would be confirmatory of the diagnosis of scarlet fever.

Q. Suppose under the circumstances you have outlined, with all of this information that a physician has in his background, he receives a report from the laboratory. Having taken a culture and submitted it to the laboratory, he receives a report indicating that he used the wrong antibiotic. What would he do then?

Mr. Trumbauer: I am going to object to that question. I think that is too general a question to ask even an expert.

Mr. Williams: Your Honor—

[193] (Mr. Trumbauer, interposing): We are speaking of every physician in the United States. If he receives a report from the laboratory that this is the wrong antibiotic, what would he do?

Mr. Williams: I will relate it to Dr. Keefer specifically.

The Court: All right.

A. Well, I would accept that information with a grain of salt, for the simple reason that if the patient respond-

ed—was responding to penicillin, which is the drug of choice in patients with beta hemolytic streptococcus sore throat, he is going to respond in about 24 to 36 hours, about the time that would be required to isolate the organism and do a sensitivity test on him in the laboratory, and this is a matter of judgment, experience and observing the patient. The information that comes from the laboratory has to be assessed on the basis of the total picture, not on just one test.

Q. (By Mr. Williams, continuing): It has been testified here that since the information obtained from the use of sensitivity test may be used as an aid in determining the presence of resistance to staphylococci among hospital personnel, or on hospital equipment, does the fact that that is so constitute the use of that information in the prevention of disease, [194] in your opinion?

A. Such information is usually collected on an epidemiological study—that is, to identify whether or not there are carriers in the community of penicillin or other antibiotic resistant stahphylococci. There are many people who carry these organisms in their nose and throat and do not have disease. Sometimes they can spread these to people who are in the hospital, or to colleagues, and in this way disease may spread through a small community; or, if a patient is admitted to a hospital, has an infection —pneumonia or wound infection, a breast abscess—that organism is isolated, identified, sensitivity tests are often done, and it is often discovered, not from the sensitivity test but from other tests, that this belongs to a particular type or major type. Then you are dealing with an antibiotic staphylococcus—antibiotic resistant staphylococcus —and from this information one attempts to determine what antibiotic it is sensitive to, and that information is used as a guide line to the employment of an antibiotic for the treatment of the actual infection, because the treatment of carriers is a very difficult business, because it fluctuates from time of year and environment.

So that preventing disease and knocking out the carriers is a very difficult matter, and, usually, has never been accomplished satisfactorily.

[195] Q. Dr. Keefer, without regard to any statutory terms or definitions, would you give us your definition of the term "drug" in the medical sense?

A. Well, a drug in the medical sense is a chemical or combination of chemicals that is used for the treatment of patients with disease or for the relief of symptoms.

Q. How do you use it?

A. By local application, orally—taking it by mouth—or by injection.

Q. Do you know of any substance which is not used in the manner you have just described which is classified as a drug in the medical sense?

A. I do not know of any.

Q. In your experience, does your answer to that question constitute from the medical and scientific standpoint the generally accepted definition of the term "drug"?

A. I believe it does, yes, sir, by physicians who use drugs for patients.

Q. Dr. Keefer, do you know whether it is customary or rare for practicing physicians to conduct sensitivity tests of the kind we are talking about?

A. I would say from the total number of infections that doctors see and treat, both in their offices and in the home, and many in hospitals, the sensitivity tests is not used. It is not used [196] routinely. The sensitivity test is usually employed in patients who have infections—complicated infections—such as urinary tract infections, who are not responding to a broad spectrum antibiotic. So the treatment is frequently changed because a patient does not respond to the initial therapy.

Q. In such a case, the information obtained from the sensitivity test might be used as one of the factors?

A. Might be used as an aid in changing or selecting another antibiotic.

Mr. Williams: Excuse me, your Honor. I need a paper.

Your Honor, one of the exhibits attached to Libelant's written interrogatories in this matter is a leaflet, which is part of the labeling of the Bacto Unidisks under sei-

zure. I have forgotten the number. Is that Exhibit 1, your Honor?

The Court: Exhibit 1 is a representative sample of the seizure.

Mr. Trumbauer: Including the literature in the box, I think, your Honor.

Mr. Williams: It is a box insert.

The Court: All right.

Q. (By Mr. Williams, continuing): Doctor, will you read the second [197] sentence in the first paragraph of this label which refers to Bacto Unidisks—the second sentence in the first paragraph.

A. The second sentence reads:

> "They are recommended as a rapid, practical, clinically accurate and inexpensive means of determining the relative sensitivity of microorganisms to these therapeutic agents."

Q. Now, will you read the last sentence in that paragraph beginning "Bacto sensitivity disks."

> A. "Bacto sensitivity disks are especially valuable in selecting the drug effective against chronic or persistent infections refractory to primary therapy."

Q. Do you consider those two statements consistent with your testimony?

A. I do.

Q. Do you consider that those two statements suggest that the disks are used in the diagnosis, treatment or prevention of disease?

A. Well, it does not suggest that to me, sir. The last sentence states that it is valuable in selecting an agent. That may be valuable, may be helpful, in chronic or persistent infections that are refractory to primary therapy. This is often done. This is the reason sensitivity disk is used, when a patient does [198] not respond to primary therapy. A sensitivity test is done to find an antibiotic that hasn't been used and is active against the organism, so that the doctor may or may not want to switch to that antibiotic, providing the patient has not responded.

Q. If you read in the medical literature a statement referring to a particular drug which said, "This drug is for use by man," what would that mean to you as a physician?

A. Just that; wouldn't be used for domestic animals; used by man.

Q. Does that mean it would be used for administration to man, or just for him to handle it in some manner?

A. For the treatment of—

(Mr. Trumbauer, interposing): Objection, your Honor. I think that is an improper question based upon the illustration that counsel gave to the witness.

Mr. Williams: I am not sure what he means by illustration.

Mr. Trumbauer: Well, the words that you gave him to comment on.

The Court: Well, I think a clarification of what the expression means would be helpful—if the witness can be given the question and would furnish that clarification.

Mr. Williams: I can ask the witness, your [199] Honor, whether the words "for use by man" mean to him, when referring to a drug, that that drug is to be taken by or applied to the patient, or whether it means that a physician handles the drug instead of something else handling it. I don't know what the "something else" might be. Is it for administration or application to the patient? Is that what it means, or does it mean something else? Does it mean the same as "for human use," for example?

A. Yes, and followed by directions as to how to use it.

Q. (By Mr. Williams, continuing): What does "for human use" mean to you in terms of a drug?

A. Well, it means the actual local application, taking it by mouth, or somebody injecting it, or injecting it yourself under direction.

Q. Is that what "for use by man" means to you?

A. That is what it means to me, yes, sir.

Q. Dr. Keefer, in your experience, have you found any situation in which sensitivity disks, or the sensitivity test, or the information obtained from the test, has resulted in the institution of life-saving measures for patients or a patient?

A. Not from that information alone, no, sir. I wouldn't say from that information alone it had resulted in instituting life-saving measures.

Q. In your experience, is there a public health problem connected with the possible inadequacy of sensitivity disks which may be [200] on the market?

A. I know of no such problem.

Mr. Trumbauer: I think the same objection applies there, your Honor, that the Court sustained a little earlier with respect to whether there is a need today for legislation.

The Court: Well, only that I do think that to some degree, at least, the door has been opened on the testimony of Dr. Truant today. You went into that quite thoroughly.

Mr. Williams: I may say, your Honor, I wouldn't have asked the question otherwise. Dr. Truant intimated, although he could give no specific examples, that a situation might arise where the test would be so inaccurate that it would result in the administration to a patient of the wrong antibiotic.

Q. (By Mr. Williams, continuing): Have you had any such experience as that?

A. We haven't had any such experiences, because in such instances where such a question may arise, the patient is usually getting one, two, three and sometimes four different antibiotics if he is desperately ill.

Q. Doctor, do you recall how long sensitivity disks have been made commercially?

[201] A. Not precisely, but I believe it was about 1949 or '50. I would have to confirm that, because I don't recall exactly when they were first made and available commercially.

The Court: We are talking about a sensitivity disk; we are talking about Exhibit 1?

Mr. Williams: Yes, sir.

The Court: Susceptibility has been used here.

Q. (By Mr. Williams, continuing): Dr. Truant seems to use the term "susceptibility," and another "sensitivity," and they are about the same. Isn't that correct?

A. That was my interpretation.

Mr. Trumbauer: We would agree with that basic conclusion.

The Court: He used that, but he used "susceptibility" quite often.

Mr. Williams: I think it should be stated in response to your question that the first disk being made which Dr. Keefer was talking about may or may not have been—I don't know, but may have or may not have been these Unidisks, with several antibiotics impregnated in it. They may have been single disks, but the problem is the same with all of them.

That is all I have.

The Court: Well, it is almost time to recess [202] for lunch. Want to start at 2:00 o'clock?

* * * *

[203] *Cross Examination*

By Mr. Franchino:

* * * *

[205] Q. And did you supervise the laboratory, or were you the clinician who received the results?

A. I did both, because in our hospital organization, the infectious disease laboratory—both the service laboratory and research laboratory are under the Department of Medicine, not under the Department of Pathology as it is in many institutions.

Q. So there is integration of the two?

A. There is integration, yes, sir.

Q. Were the results of the disk tests you performed or supervised used to any extent to select antibiotics to be administered to the patients?

A. When indicated.

Q. What percentage of the time would this be indicated? Would the choice of drug be indicated by the results of the susceptibility disk test?

A. About one out of five patients, perhaps.

Q. About 20 per cent of the time?

A. Twenty per cent.

Q. I see here, Doctor, you have written many articles and two books dealing with the study and use of antibiotics; is that correct?

A. That is correct.

* * * *

[218] Dr. Keefer, is it customary when performing routine susceptibility testing with disks to use what they call the high-potency and low-potency disks?

A. Yes.

Q. Could you describe to me briefly, if it is possible, how this is done and what you understand by the term "high-potency disk" and "low-potency disk"?

A. Well, the disk is considered to contain varying amounts of the given antibiotic. Low-potency disk may contain two units—two micrograms. A high-potency disk may contain ten or five, or it may be ten or 30.

Q. This would be of the same chemotherapeutic agent?

A. Yes.

Q. Then, I take it, what you actually have is the performance of two separate tests?

A. Well, you use two disks, one containing a small amount and another containing a larger amount. They are both placed on the plate that contains the organisms that have been identified. This is incubated in an incubator at 37 degrees centigrade for 18 hours, and then the plate is removed from the [219] incubator, and one looks for the clear zone around either one of these disks.

Q. Now, suppose that we would find a larger zone around the higher potency disk and a smaller zone around the lower potency disk, would that be of any significance to you?

A. Well, it would mean that more antibiotic diffused out from the disk in the higher potency than in the lower potency.

Q. Would this serve as any guide line to you in the administration of a particular drug?

A. I would say that the organism was highly sensitive.

Q. What conclusion would you reach, Doctor, if the zone of inhibition—and I assume that although the po-

tencies on the two disks differ, this actual physical size of the disk is the same; correct?

A. Yes.

Q. Thank you. What would be the significance to you, Doctor, in reading the results of the disk test run with a high disk and low disk, if the zones of inhibition were of equal size around the low disk and the high disk?

A. It was sensitive—the organism was sensitive.

Q. Would that affect your judgment with regard to the dosage of the drug?

A. It would not.

Q. What would it mean to you, Doctor, if the zone of inhibition [220] around the low disk were larger than the zone of inhibition around the high disk?

A. Well, I would say that the organism was sensitive, as I had before.

Q. And what would you say, Doctor, if there were a larger zone of inhibition around—if there were a zone of inhibition around the low disk and no zone around the high disk?

A. Well, I would want to take a look at the container from which the high disk was taken, whether somebody left the top off the bottle or not. I would want to run the test again.

Q. You would question the disk?

A. I would question the test, yes—the results of the test.

Q. You would question whether or not the tests were performed properly, I presume.

A. Yes, that is correct.

Q. You would also question whether or not the disk contained the amount of antibiotic that it purported to contain; is that correct?

A. Well, a sufficient amount of antibiotic to inhibit the growth of the organism.

Q. Now, if the zone around the low-potency disk were larger than the zone around the high-potency disk but yet you still had two zones, obviously, would you still question the performance of the test, the methodology?

A. No, I would say the organism was sensitive.

[221] Q. Do you see this frequently, where there would

be a larger zone of inhibition around the low disk than around the high disk?

A. No, they are usually very often the same in the sensitive organism.

Q. Now, I think you stated that if a person were suspected of being a carrier of a particular disease—I read last week in the Washington Post that they found a diphtheria carrier, and that individual worked in a hospital—did I understand you to state this morning that sensitivity disk test may be performed on specimens taken from the suspected carrier, with the view toward selecting the drug to which the organism is most sensitive?

A. Yes, that is one method.

Q. And that the treatment, and hopefully the cure, of the carrier would assist in the prevention of the further spread of that disease in the area in which he may be employed?

A. It might.

Q. Are we talking about carriers where the carrier himself does not know he is a carrier?

A. Yes, sir. They are often referred to as asymptomatic carriers.

The Court: And nothing has happened, apparently, in their lifetime which would indicate they were carriers?

A. Yes, sir.

Q. (By Mr. Franchino) Now, you stated that sensitivity testing was useful as a guide line to treatment, and that it was one [222] of the many guide lines to be utilized by the physician in the treatment of the patient; is that correct?

A. That is correct.

Q. I take it, then, you are concerned that we don't blow out of prospective or over-amplify the significance of sensitivity disk testing on the selection of the drug; is that correct?

A. That is correct.

Q. And you feel that view is consistent with the last sentence in the first paragraph of the package insert which reads:

"Bacto Sensitivity Disks are especially valuable in selecting the drug effective against chronic or persistent infections refractory to primary therapy."

Is that correct?

A. That is correct.

Q. May I add something to this?

"Because these are the situations in which sensitivity tests are of greatest help to the doctor."

A. If you have a chronic, persisting infection that has been refractory to what treatment you have been using.

Q. Refranctory, being stubborn?

A. Stubborn; the patient hasn't responded as you anticipated and continues to have fever, continues to have organisms in the urine, if it is a urinary infection, or in the womb if it is a womb infection.

[223] Q. So the use of sensitivity disks in selecting a drug where primary therapy has already been started is a relatively more important guide line than the routine performance of disk testing in all patients or all cases that may come into an institution; is that correct?

A. That is correct.

Q. So when you say it is a guide line, it is a more important guide line in the physician's armamentarium in certain cases than it is in others; is that correct?

A. Yes.

Q. I noted this morning in response to a question from counsel, you indicated that no specific experience was had by you where the wrong drug was given as the result of bad disk or a dud disk. Have you had any general experience as opposed to specific experience?

A. No, none whatsoever.

Q. Using, for a moment, your concept of the disk as a laboratory agent, can you think of any laboratory agent containing a chemical which used as a guide line to treatment, where a drug corresponding to that chemical will ultimately be used in the treatment of the patient—that is, administered, applied, injected to a patient?

A. I don't recall of any now, at the moment.

Q. The sensitivity disk would be the only example; is that [224] correct?

A. The results of the sensitivity test might be a guide line to treatment.

Q. Do I understand you correctly, then, Doctor, that the distinction you draw here is that whereas the information or the results of a test performed with sensitivity disk may be used in the treatment, or as a guide line to treatment, the disk itself is not used as a guide line or in the treatment; is that correct?

A. That is correct.

Q. That is the distinction that you draw?

A. That's right.

Q. Dr. Keefer, I am a little confused about the role of the disk in the identification of a disease organism. Perhaps you can enlighten me. Is it so that if we have an organism which has been tentatively identified as streptococcus, that if a bacitracin disk is used to perform a disk test, or sensitivity or susceptibility test, with the organism, that a presumtive identification of the organism will be made as to group—that is to say, a physician may determine or conclude that the offending organism is of group A streptococcus as a result of his observation of the test performed with the bacitracin disk? Is my understanding correct?

A. Let me answer your question this way: 95 per cent of all human infections are due to group A beta hymolitic streptococcus. [225] The others are groups that are assigned with letters: B, C, D, E, F and G, and down to H. So that the exact identification of Group A hemolytic streptococci requires the use of specific sera, specific grouping sera, that is made by taking a group of hymolytic streptococci, such as you acquire from scarlet fever, and injecting that repeatedly in the rabbit until the rabbit develops an antiserum, and you take this antiserum and test against it. That is the way you identify group A beta hemolytic streptococcus.

* * * *

[227] *Redirect Examination*

By Mr. Williams:

Q. You have been asked a number of questions about whether certain substances intended for administration or ingestion by humans are drugs. Do you recall that question?

A. I do.

Q. Do you happen to know whether substances intended for use, or labeled for use, in the diagnosis of disease are drugs within the meaning of the Food, Drug & Cosmetic Act?

A. I do not know whether all of them are placed in this category [228] or not.

Q. Do you regard the labeling of the Unidisks, which you have seen on two occasions today, as constituting any claim that these disks are intended for us in diagnosis?

A. No, sir, I do not interpret any statement that I have read in that package insert in that sense.

Q. Do you interpret that labeling as applying or suggesting that these disks are for use in treatment?

A. No, sir.

Q. Or for use in the prevention of disease?

A. No, sir.

Q. Or the mitigation or cure of disease?

A. No, sir.

* * * *

[229] Q. Doctor, you stated, in answer to a question, as I recall it— [230] correct me if I am wrong—that a stethoscope is used in the diagnosis of disease; is that correct?

A. Yes.

Q. What does the doctor learn from the use of the stethoscope?

A. Well, he hears sounds that are transmitted from the heart, or the lungs or the intestine. There are always normal sounds that come from the normal heart, the normal lungs and the normal intestine. So when he applies the stethoscope and hears abnormal sounds, or extrinsic sounds like a heart murmur, this, taking it together with other findings in examination, may indicate that he has a valve that is insufficient.

Q. How would you distinguish, if you would, between the information obtained from the disk test and that obtained from the stethoscope in the context of the question whether or not the information from the disk is used in diagnosis, and whether or not the stethoscope is used in diagnosis?

A. Well, I think the stethoscope is used as an aid in diagnosis, and the sensitivity disk is not used as an aid in bacteriological diagnosis. The test is the sensitivity of the organism to the antibiotic disk.

Q. Does the information you obtain from the stethoscope help you to identify the probable cause of the patient's disease?

A. Yes, it does, in some instances.

Q. Does the information you obtain from the disk test help you [231] to identify the organism causing the patient's disease?

A. Does not help to identify the organism. It helps to identify the sensitivity of the organism.

* * * *

[234] DR. ALBERT MARTIN LERNER was thereupon called as a witness by the Libelant, and after being duly sworn, testified as follows:

Direct Examination

By Mr. Trumbauer:

Q. You are Albert Martin Lerner?

A. That's right.

Q. And your address, sir?

A. 1009 Lafayette Towers West, Detroit.

Q. What is your occupation, Doctor?

A. I am associate professor of Medicine, and associate professor in Pathology and Microbiology at Wayne State University, School of Medicine.

Q. Do you also have any hospital affiliations?

A. Yes. I am chief of Infectious Diseases and director of the Bacteriology Laboratory at the Detroit Receiving Hospital. I am a consultant in Infectious Diseases to the Dearborn Veterans Administration Hospital. I am consul-

tant in Infectious Diseases to several other hospitals in this city, and am called upon regularly by the State to teach clinical infectious [235] diseases about the state.

Q. Would you give us briefly what your education has been—medical education?

A. I graduated from Washington University, School of Medicine, in 1954. I interned in Medicine at Barnes Hospital in St. Louis for one year.

I then went to the National Institute of Health in Bethesda, Maryland, and did laboratory research in Virology and Epidemiology in the National Institute of Allergy and Infectious Diseases in Bethesda.

I then went to the Harvard Medical Unit at Boston City Hospital in 1957 and took a residency in Medicine in that unit.

I then returned to St. Louis for a senior residency in Medicine for one year.

I then returned to the Thorndyke Memorial Laboratory at Harvard Medical School in 1959 to establish a virus laboratory under the supervision of Dr. Maxwell Finland. I stayed there for a period of four years directing that laboratory, and the research of that laboratory, and being completely in charge of research in antibiotics right next door, in Dr. Finland's laboratory. There I regularly for four years was consultant in Infectious Diseases to the Boston City Hospital.

[236] I then continued to work at the City Hospital and went over to continue my research at the Massachusetts Institute of Technology at Cambridge. I was there for one year as research associate and continuing my association with Harvard at the City Hospital teaching Medicine, and continuing to work in infectious diseases.

I then left there to take my present position.

Q. During this period, Doctor, have you been engaged in the publication of any papers or reviews, either by yourself or jointly in connection with your specialized field?

A. Yes; I haven't counted them recently, but thirty-some original publications with myself and colleagues, a

number of them over the past year and a half, since I have come to Detroit.

Mr. Trumbauer: Will you mark this as No. 6, please?

(A statement of Dr. Lerner's background and qualifications was marked Libelant's Exhibit No. 6 by the Reporter.)

Q. (By Mr. Trumbauer, continuing): Doctor, will you look at this document which I have marked as Exhibit No. 6, and tell me if it represents an accurate summary of your education, work history, and the publications that you have been involved in as you gave oral testimony to?

A. It looks reliable.

Mr. Trumbauer: I will offer this as Exhibit No. 6 in support of Dr. Lerner's qualifications to testify.

Mr. Williams: No objection.

* * * *

[238] Q. Now, in your work, then, do you become involved in the area of sensitivity, disk testing, or the area of sensitivity test- [239] ing as a whole?

A. It is impossible to deal with a sick patient with an infection without dealing and grappling with disks and the results of these disks.

Q. I see. Now, do you actually run, under your general supervision, these sensitivity tests? Are these sensitivity tests run at the hospital?

A. Yes, they are.

Q. And approximately how many on the average are run, say, every month?

A. I would estimate, without having really checked this, that somewhere between 500 and 1000 are run each month in the laboratory.

Q. Now, are there other methods of testing for sensitivity to antibiotic drugs besides the so-called disk method?

A. Yes, there are.

Q. Just before we get into that, just for the record, I want to show what has been marked Exhibit 1 to you; a portion thereof, and ask you if you can recognize what that item is?

A. Yes. This is a circle of paper on which there are certain circular objects, antibiotics and sulfonamides—a sulfonamide and the rest are antibiotics—that are impregnated thereon.

Q. Do you recognize it as the same type of product that is used in the sensitivity disk area that you have described?

[240] A. It may be used. We don't use this particular one, but it may be used.

Q. Now, I take it—I am not trying to lead you here but to speed it up—you take isolates, as they say, I believe, from patients and test them with this disk; is that right?

A. This is correct, yes.

Q. What happens then, after you conduct the test?

A. Well, firstly, in our laboratory, and in others as well, the test itself, using the particular agar and the particular salt concentration, must be standardized. So in our laboratory several years ago we used the agar that we were going to use and took a number of isolates and measured the zones and divided the zones into three groups that they feel, and we could feel, were qualitative assurance that the largest disk zone of inhibition for a particular antibiotic—and the zone varies depending upon the difusion potentials of the several antibiotics—we could then separate the organisms into those that were more likely sensitive, those that were in the intermediate range of sensitivity, and those that were probably resistant.

Q. Once having gotten that information, what do you normally do with that information?

A. This information then is recorded on a record in millimeters and sent to the physician.

[241] All of our residents in the hospital have the results, the mean results, and the deviations of these multiple tests run over several months, and then the physician caring for the patient interprets the results of this laboratory procedure.

Q. I see. With respect to the disease that the patient may have?

A. With respect to the isolate isolated from the patient. The interpretation of whether this isolate causes a disease is another problem entirely, which is a clinical problem left to the judgment of the physician.

Q. But does he use this information as part of his ultimate determination?

A. He may use it, or he may discard it. If it turns out that it does not fit with the multiple of other data that he receives, he may choose to repeat it or discard it. If it aids and abets his judgment, he may use it and often does.

Q. Now, you indicated that several years ago you set up certain standardization in your laboratory so you could grade these results; is that correct?

A. This is correct.

Q. By sensitive, slightly sensitive, and resistant; and for each antibiotic?

A. Yes.

Q. Now, do these antibiotic sensitivity disks come to you from [242] the source that you buy them in a certain concent the disk?

A. Yes, they do.

Q. What do you mean by that?

A. Well, I mean that there are disks that come at one level of impregnation, which is important, and another disk may come at another level of impregnation. It is important not only that the level be the level that it says that it is, but also that that level be a proper level which is obtainable within the tissues and fluid of the infected patient, if this be the case.

Q. Why do you say it is important that this level be as it is represented to be?

A. Because at levels which are unobtainable in the body, either because of the toxicity of the particular agent, or because of its absorption, a laboratory procedure—the test in question—may or may not be a reasonable test for the patient. If the level is too high, it may indicate a sensitivity or usefulness which is indeed not really operatable within the situation in question.

Q. You mean if the concentration on the disk is higher than what is represented on the disk?

A. No; it might be exactly the concentration that is represented, but it may be at a level where the agent or the drug may be [243] toxic to the patient. So this may not be a practical test for the patient. The level has to be that which is represented; and it must also be at a practical level for the physician and concerning the rest of the pharmacology and safety of this drug.

The Court: May I have this answer again?

(The answer was read by the reporter.)

Q. (By Mr. Trumbauer, continuing) Well now, you have stated you used certain testing procedures in connection with this whole operation. Are you able to utilize in your hospital testing procedures with regard to the concentration that is represented on those disks?

A. I am unable to do this, Mr. Trumbauer.

Q. Why is that?

A. Our situation is very much like the situation in most hospitals in this country, particularly municipal hospitals. We are understaffed, we are underspaced. We have enough to do, or as much as we can do to ask our people to do the routine concerning the care of patients and the work in the bacteriology laboratory. To ask them to standardize an antibiotic disk would be more than they would be capable of doing and more than I could ask them to do.

Q. Now, in connection with the running of the test, how important do you feel that the accuracy of the represented concen- [244] tration is?

A. I feel that it is vital.

Q. Why is that?

A. Because I cannot take this disk in the bateriology laboratory and test its accuracy. I take it as prima facie —accept it as shown when I accept the disk.

Q Could you tell us what might happen where a disk contained, for example, more of antibiotic than is represented by the product?

A. This might be conjecture as to what might happen, but, certainly, if the amount of antibiotic varied from time to time, the laboratory interpretation of these tests would be thrown completely out of kilter.

Q. Do you feel, then, based upon your training and experience and your work, and the work that you do in this area, that there is a matter of the public health involved in making sure that these disks are accurate within reasonable limits?

A. Yes, I do feel this, and my major reason for feeling this is that in my laboratory, and in my other laboratories, we have no internal standard of these disks. We cannot run a control as to the accuracy or strength of these disks. Therefore, I feel it is important to have some control, some standard that we know and can accept when we receive these disks.

* * * *

[245] Mr. Trumbauer: I have no further questions.

The Court: All right.

Mr. Williams: Your Honor, could I have a five-minute recess? I don't think I will have many questions.

The Court: All right, five minutes.

(A short recess was taken.)

The Court: You may proceed.

Mr. Trumbauer: We found the literature, your Honor. I am not looking for the literature.

Mr. Williams: Shall I proceed, your Honor?

The Court: Yes, go ahead.

Cross Examination

By Mr. Williams:

Q. Dr. Lerner, you stated it is vital that the concentration of the disk be as represented on the label. Suppose the concentration were off 10 per cent. Would that make a difference in the validity of your test result?

A. I don't know, sir.

Q. Suppose it were off 20 per cent?

A. I don't know, sir.

Q. Suppose it were off 40 per cent?

A. Not having standardized these disks when they were off such a percentage, I would not know, sir.

[246] Q. Have you determined that the variation between the actual concentration and that on the label affects the end result of the test?

A. Have I determined? In an offhand sort of way. For instance, penicillin disk which was 5 units against a sensitive organism would have a smaller inhibitory zone than a disk which had ten units, twice that much. In so far this is a test of the standard and the amount of the drug on the disk, I have made such a determination.

Q. You stated, did you not, that if the amount of antibiotic varied from time to time, the laboratory interpretation of the test would be thrown out of kilter.

A. It might. It seems to me reasonable to assume that there is a level of variation beyond which the test results would be markedly altered.

Q. You don't know what that level would be?

A. No, I do not, sir.

Q. Did you not state that the public health was involved here?

A. I feel that it is, sir.

Q. Have you had any specific experience showing that a patient has been harmed as a result of a test with a faulty disk?

A. I have not had such experience. However, there have been results of tests which have occurred in my hospital and hospitals which were formerly my hospitals which I have dis- [247] carded because they were not coincident with the rest of the information concerning the condition of the patient in question.

Q. This is information you have discarded from the disk test?

A. Yes.

Q. Do you mean, for example, that if you have started the administration of an antibiotic or chemotherapeutic agent to a patient and thereafter you obtained the results of a sensitivity test which indicated that the antibiotic which you were giving was the wrong one and yet that it is improving the condition of the patient, that you ignore the test? Is that what you mean?

A. I mean, in the situation where the patient is improving and improving according to the way we would

like him to improve, regardless of, I would be very prone to disregard any laboratory test, be that a chemical test of real function or antibiotic disk, or whatsoever it might be.

Q. "But you don't necessarily know that the reason the test shows that the antibiotic that you have chosen the wrong antibiotic was the faulty concentration, do you?

A. There are so many variables concerned in this question, the interpretation of these disks is a tremendously complex one. So there is really no answer of this question unless we speak for several hours.

* * * *

[248] *Redirect Examination*

By Mr. Trumbauer:

Q. Have you also found instances where you would, or the physician with whom you were working, would change the treatment based upon the results or information obtained from the disk test?

A. There is no question about that. That in a patient with an infectious disease, where the physician feels on the basis of multiple evidence that this is an infection, that the infection is due to the bacterium isolated, there is no question that frequently therapy may be modified as a result of [249] the interpretation of this test.

The Court: I don't know whether that was your question or not, to be honest about it. He has qualified his answer with the doctor being in the possession of multiple evidence. I though you were asking just about the results of a disk test.

Q. (By Mr. Trumbauer, continuing) Well, assuming, Doctor—let's tal as an assumption—that the doctor uses the disk test as only one of perhaps several areas by which he makes his final conclusion. Is that right, the doctor may use the results of the disk test?

A. Concerning the sensitivity of this bacterium in this disease situation, the antibiotic disk may be the only laboratory test, and often is the only laboratory test used.

A. I see. You mean it is more heavily relied upon in the area of infectious diseases than some other areas?

A. Where properly applied in the therapeutic situation of an infection due to a bacterium, it may be of paramount importance.

Q. And, of course, the doctor takes the results of that test and must always apply his own total judgment; isn't that right, or should usually apply his total judgment?

A. This is correct.

Q. But assuming that, are there instances where he would, as a [250] result of the information received, make a change in the therapy that he has perhaps already started on?

A. There is no question about the fact that therapy is frequently modified or altered as a result of these tests.

The Court: Anything further?

Mr. Williams: Yes, if I may.

Re-cross Examination

By Mr. Williams:

Q. Do you know what strain of bacteria causes most human infections?

A. No, I do not, sir.

Q. You do not?

A. I don't know what you mean by most human infections. There are various infections. I am familiar with a number of them.

Q. What is your practice? Do you ordinarily at least make a temporary diagnosis of a patient with an infection and start therapy and then invoke the isolation and testing procedures?

A. No, that is not quite the way we do it. When we see a patient with an infection, we attempt to make a diagnosis first. This diagnosis may involve the use of a physical diagnosis, history as well as the patient can give it to us, certain simple laboratory procedures such as the staining of the sputa, contents of infected chest fluids looking for these [251] bacteria, looking at the temperature and white blood count, and a number of other things. Then the cultures are taken in our hospital hopefully before treatment is started, and then a presumtive diag-

nosis is made, so that therapy is begun before an absolute diagnosis is made frequently.

Q. Is frequently or usually begun before the sensitivity test is completed?

A: It is almost always begun before the sensitivity test is completed.

Mr. Williams: Thank you, sir.

Mr. Trumbauer: Thank you, Doctor Lerner. I have no further questions.

(The witness was excused.)

Mr. Trumbauer: We have no further testimonal evidence to offer, your Honor, in connection with our direct case.

The Court: Do you rest, then?

Mr. Trumbauer: We rest.

Mr. Williams: Your Honor, there are two additional witnesses for the claimant. I would estimate that—

The Court (interposing): You want to quit now, is that it?

Mr. Williams: I should be frank with your Honor, [251-A] yes.

[252]

Detroit, Michigan,
Thursday, May 20, 1965,
9:30 o'clock A. M.

(Court convened pursuant to the adjournment.)

The Clerk of the Court: United States v. an article of Drug, and so forth.

The Court: All right, Mr. Williams.

Mr. Williams: I will ask Dr. Miller to come to the witness stand.

DR. LLOYD C. MILLER was thereupon called as a witness on behalf of the Claimant and, having been first duly sworn, testified as follows:

Direct Examination

By Mr. Williams:

Q. Will you state your name and address, Dr. Miller?

A. I am Lloyd C. Miller. My office address is 46 Park Avenue, New York.

Q. Dr. Miller, what is your present occupation and position?

A. I am Director of Revision of the United States Pharmacopeia.

Q. Could you give a sketch of your educational background?

A. Yes. I received my college training at Pomona College in [253] California, leading to a B.A. in 1929. Continued into graduate school at the University of Rochester, School of Medicine and Dentistry, leading to a Ph.D. in 1933.

Q. In what?

A. A Ph.D.—in 1933.

Q. In what subject?

A. In Biochemistry and Pharmacology.

Q. Thereafter, what was your experience, Dr. Miller?

A. I was a Research Fellow at the Upjohn Company for two years following my graduation from Rochester.

In then spent eight and a half years at the Food & Drug Administration in Washington, and followed by six years as a Director of the Biology Division at Sterling-Winthrop Research Institute.

Q. What was your position with the Food & Drug Administration?

A. I was pharmacologist and in charge of the biological assays of several of the hormone products.

Q. Have you received any awards as a result of your work?

A. Yes. I received an Ebert Medal in 1939, which is considered to be the highest scientific award of the American Pharmaceutical Association, and just recently an

award from the same association for scientific achievements in drug analysis.

Q. You had begun to tell us about an association with Sterling-Winthrop.

[254] A. Yes. I was there from 1943 to 1950, and during the first months I was there, I was in charge of the control testing of penicillin, and subsequently entirely in research.

Q. And thereafter?

A. Since 1950 I have been with the Pharamacopeia in New York, and my duties with the Pharamacopeia are to direct the revision program and to see that the U.S.P. appears on schedule every five years.

Q. Have you been associated with any international organizations in any way?

A. Yes. Since 1951 I have been on an advisory panel for the World Health Organization that is concerned with the production of an International Pharamacopeia, and I have made a considerable number of trips to Geneva for work on that committee.

Q. Have you had anything to do with drug standards on an international scale?

A. Yes. As a result of my work with the International Pharmacopeia, I head a committee here in the United States which is called the United States Committee on International Drug Standards, the purpose of which is to get comments from those in the United States on the standards that are proposed for international use in International Pharmacopeia.

Q. Do you have anything else to add, Dr. Miller?

A. No, I don't believe so. I have published about fifty papers, [255] if that is—

Q. (Interposing): That is relevant. In the field of—

A. (Interposing): Yes. In drug analysis.

Q. In drug analysis?

A. Yes.

Q. Is this an accurate biographical sketch? (Handing document to the witness.)

A. Yes, this is.

Mr. Trumbauer: May I have this identified as Exhibit No. 7.

(A document entitled, "Biographical Sketch, Lloyd C. Miller, Ph.D.," was thereupon marked Claimant Exhibit 7 by the Reporter.)

Mr. Trumbauer: No objection to its admission, your Honor.

The Court: It is admitted.

Q. (By Mr. Williams, continuing): Dr. Miller, what is the United States Pharmacopeia?

A. The U. S. Pharmacopeia is a book of standards which is published every five years. The information in it is determined by a selection of drugs represented to be the best teachings and practice of medicine. And, for those drugs that are selected, standards of purity and potency are provided, and methods are provided for determining compliance with those [256] standards.

In connection with that, we have—we require a description of a great number of reagents used in the tests that are described, so we provide standards for the reagents as well.

Q. Dr. Miller, what is the United States Pharmacopeial Convention?

A. That is the organization which gives authority to our work. It was organized in 1820. It was incorporated in 1900.

It is one of the oldest organizations of its kind in the world. It has been in continuous existence, and it is unique in many ways, namely, in that it consists of an organization of private individuals, scientists, medical men.

The convention itself is composed of delegates, one from each school of medicine, one from each school of pharmacy; there are eight national pharmaceutical associations; a limited number of other national associations; and some departments of the government.

This convention is brought together each ten years in the years ending in zero. That is, "1960," "1970," and the next one. And it elects a committee, a committee of experts, twenty of whom are physicians, or related to the medical practice; forty—making sixty in all—are chemists, pharmacists, bacteriologists, the purpose being, in selecting this committee of sixty, to provide my office with every

kind [257] of skill that would be expected to be required in producing the two issues of the Pharmacopeia in the ten years following the election of the committee.

Q. Specifically, what is the principal function of this committee, and what is it called?

A. It is called the U.S.P. Committee on Revision, and its function is to select the drugs that go into Pharmacopeia and provide standards for them.

Q. Did you say it was elected by the convention?

A. Yes, it is.

Q. What revision of the United States Pharmacopeia is now current, Dr. Miller?

A. The 16th Revision. It took effect in 1960 and will have effect until September of this year.

Q. Is there another Pharmacopeia imminent?

A. Yes. I am proud to say the next one came out last week and will take effect when this new one—the new one supercedes the present one in September.

Q. Did you say the U.S.P. 16 is the one which is now effective?

A. Yes. 17 is the one that is coming up.

Mr. Williams: Your Honor, I assume, since the United States Pharmacopeia is an official compendium under the Food, Drug, and Cosmetic Act, that judicial notice will be taken of it; that we need not introduce it as an exhibit in [258] order to use it in the testimony of Dr. Miller.

The Court: Well, is that the same publication that is mentioned in the statute?

Mr. Williams: Yes, sir. It is one of the three mentioned in the statute.

The Court: Yes.

Mr. Franchino: I should think, however, your Honor, if the Court does not have a copy available for reference—

The Court (interposing): No.

Mr. Williams: I was going to offer your Honor a copy.

The Court: All right.

Mr. Williams: Also, the National Formulary, which is another of the three listed.

Q. (By Mr. Williams, continuing): You have a copy of U.S.P.-16—

A. (Interposing): Yes.

Q. (Continuing): —do you not?

A. Yes.

Q. Will you please read the first paragraph or statement under "History of the Pharmacopeia" on page XXV, beginning, "It is the objective of a Pharmacopeia"?

A. (Reading):

> "It is the objective of a Pharmacopeia to select from among substances which possess medicinal power, [259] those, the utility of which is most fully established and best understood; and to form from them preparations and compositions, in which their powers may be exerted to the greatest advantage. It should likewise distinguish those articles by convenient and definite means, such as may prevent trouble or uncertainty in the intercourse of physicians and apothecaries."

Did you ask only for the first paragraph?

Q. Yes, I think that is sufficient. Will you tell us, from looking at this page XXV, Roman numeral, what the source of this sentence was?

A. It came from the preface of the very first Pharmacopeia, which came out in 1820, and it is almost astounding how clearly that which was written in 1820 describes the present function of the Pharmacopeia in 1965.

Q. Does that statement, then, convey the basic policy regarding admission of drugs to the U.S.P.?

A. Yes.

Q. Including U.S.P.-16 and the forthcoming one?

A. That is right.

Q. Dr. Miller, could you give us an idea, more specifically, of what the criteria for admission to the U.S.P. are?

A. The criteria are difficult to state, but the best, most succinct statement of them that I have been able to come up [260] with is that the article selected shall represent the best teaching and practice of medicine. That means that they are essential to the practice of medicine and valuable to the clinician in his treating of the ill.

In order to make these best drugs available in the form which will be useful and allow them to exert the best effect, we must provide standards also for a number of what we may speak of as pharmaceutical adjuncts, the use of which is needed to reduce a very potent drug to a form that a physician can use.

So that our admissions policy extends, then, not only to articles which we may regard as the active drug but to things which are inert, and that is why they appear in the Pharmacopeia, so that—

Q. (Interposing): Where do these inert substances appear?

A. They are in the monograph section as well.

Q. Will you explain to the Court what the monograph section is, please?

A. Yes. The monograph section is the bulk of the book. In this issue it takes up the pages from, I think, page 13 to about 811. And we speak of each section appearing under a title in large type as being a "monograph," and the large-type titles are the articles that are official in the U.S.P. They are the U.S.P. drugs.

[261] Following this monograph section, to complete the distinction of it from the rest, is a section that we designate as "Section on General Tests," in which, as the name implies, procedures that are used frequently, or are called upon frequently in the tests set forth in the monograph, are described.

And then, following this presentation of the general tests, there is another section on what I spoke of as the reagents, the chemicals that are needed to carry on these tests.

Q. Dr. Miller, what is the basic and most important criterion to which the U.S.P. looks in order to determine whether it will even consider a substance for admission to the Pharmacopeia?

A. I think the single criterion that we depend upon most is that of essential value in respect to the treatment of disease; that is, an effective agent, an agent of essential value for the treatment of disease.

Q. And in the Pharmacopeial sense and in the usage

adopted by the Committee on Revision, the authoritative body involved, what is a drug?

A. A drug is a substance used in or on a person or—I like to include a useful animal—for the treatment of a state of disease or injury.

The Court: For what?

[262] A. For the treatment of a state of disease or injury.

Q. (By Mr. Williams, continuing): Would any substance which does not come within that category you have just described be considered for admission to the monograph section of the Pharmacopeia?

A. Strictly, no. We have described agents, diluents, but they are used in the treatment of disease in the sense that the active ingredients must be incorporated with them so that they go along into the patient.

Even water, for example, is described in the Pharmacopeia, because a solution prepared for injection—solution of a drug prepared for injection is prepared in water, and the water must be of a specified purity.

Q. Did you hear Dr. Keefer's testimony yesterday?

A. Yes.

Q. Did you hear him say that in his opinion from the medical standpoint, the standpoint of a physician, that barium sulfate was not a drug?

A. I did.

Q. Is barium sulfate listed in the monograph section of the Pharmacopeia?

A. It is. And our Committee on Revision regards it as a drug, and I happen personally to. I thought it was very interesting that we happen to have a highly distinguished physician from Boston. [263] a colleague of Dr. Keefer's, who is on our Committee on Revision, and he happens to have just about the same—

Mr. Franchino (interposing): Objection, your Honor, as to what opinion the other doctor has.

The Court: I think it would be hearsay. Sustained.

Q. (By Mr. Williams, continuing): Dr. Miller, I think we should make it clear that in your position as Director of Revision you are qualified to testify with respect to the policies of the Pharmacopeia.

A. Yes.

Q. To that, and within that area, I think I can properly ask you: Is there always agreement among members of your Revision Committee with respect to what goes into the Pharmacopeia?

A. Well, they agree ultimately, although we don't have —we don't require unanimous vote.

No, there is not always agreement. There are some that are much more conservative than others.

Q. Is there a basic policy which is followed with some deviation of this sort?

A. Oh, yes. Which I have tried to state.

Q. The quotation which you read from the page designated XXV in Roman numerals refers to the selection of substances which possess medicinal power for admission to Pharmacopeia. What [264] does that term—actually the word used is "select."

A. Yes.

Q. What does the term "select" or "selection" mean in terms of a listing of articles in the United States Pharmacopeia?

Mr. Franchino: Objection, your Honor. I think the meaning of the term "selection" does not require enlightenment by an expert. I think we can take judicial notice of what the word "select" means. We are dealing here with the English language, and I think it is clear to everybody.

The Court: We are dealing with the English language in a specialized area, however.

Mr. Williams: Your Honor, may I say that I am only asking him to interpret the use of that term in this particular context. It doesn't mean what it might seem to mean on the surface.

The Court: I think the testimony is relevant. Go ahead.

Q. (By Mr. Williams, continuing): What, in terms of the policy of the Revision Committee does that term mean?

A. It means that we shall select the articles which are to be described in the monograph section. That is the—

The Court (interposing): You mean, by "we," the committee?

A. The committee, yes.

[265] Q. (By Mr. Williams, continuing): Are you distinguishing between the monograph section and some other part of the Pharmacopeia?

A. Yes. There is another section in which we describe—I think it is five articles—that—

Q. (Interposing): Are you talking about the General Reagent Section?

A. I am talking about a section which we describe as "Adjuncts and Clinical Reagents" within the General Section.

Q. Is any other word than "selected" used, or "to select" used to convey the same meaning?

A. Yes. Several words are.

Q. What are those?

A. "Admitted" is another synonym of "selected." "Recognized" is another synonym. And even occasionally the word "listed" is used, although we make a distinction in our thinking because, strictly speaking, reagents are listed but they are not—they haven't been selected. They come in simply because they are needed. No selection process is involved in putting them in.

Q. And those terms mean selected or admitted to what portion of the Pharmacopeia?

A. The monograph section.

Q. Under the heading "General Notices Applying to Standards, Tests and Assays" on Arabic page 1, would you read the sentence [266] beginning "Articles listed herein are official"?

The Court: What page is this?

Mr. Williams: Page 1, Arabic numeral, under the heading "General Notices."

The Witness: It follows Roman numeral page XLIV.

A. This sentence is in a section, the subheading of which is "Official," and it is the last sentence of three in that section, and it reads:

(Reading):

> "Articles listed herein are official and the standards set forth in the monographs apply to them only when the articles are intended or labeled for medicinal use

and when bought, sold, used or dispensed for this purpose, or when used in the tests and assays herein provided."

Q. (By Mr. Williams, continuing): Do you remember whether that sentence is the same in the forthcoming Pharmacopeia which will become effective September 1?

A. Yes, I do remember, and I happen to know that the last phrase of it—

Q. (Interposing): Beginning with what word?

A. "or when used." (Continuing with previous answer) —does not appear in the new revision. I have a penciled note to the [267] effect a question has arisen, does this mean that the standards apply to reagents, and, when we took that up with the committee, the decision was that it was not intended that the reagents are to be considered official articles. And, therefore, the committee in its judgment left this last phrase out in the new edition.

Mr. Franchino: I move to strike that answer, your Honor.

The Court: I will strike it. I don't think we should involve ourselves with something that isn't yet in being. We are not going to get over in the psychic area.

Mr. Williams: It is in being, but not—

The Court (interposing): It is not in being, because the witness said it isn't out until September.

The Witness: I am sorry. I have a copy here.

The Court: Your testimony is that this would be published in September, as I remember it, and until September comes that is not in being as far as I am concerned.

The Witness: May I have permission, please to correct an essential point?

We are required by custom, and I think even the Food & Drug would insist, that we get out this book several months before; "allow a reasonable time" is the wording, I think, that this shall be published; a reasonable [268] time before it takes effect. And, if I—

The Court (interposing): Well, that makes it all the more objectionable, since you said "before it takes effect."

A. Yes. It takes effect on the first of September. The book has now been published.

The Court: Until the first of September it doesn't have any value around here, as far as I am concerned.

Q. (By Mr. Williams, continuing): To what drugs do the words "articles listed herein" refer in the quotation which you just read?

A. The articles in the monographs.

Q. Those in the monographs?

A. Yes.

Q. Are any drugs official other than those in the monographs?

A. May I ask you, you are confining it to U.S.P.?

Yes, there are other drugs official other than in the U.S.P.

Q. No. I mean are any drugs official in the Pharmacopeia other than those listed in the monograph?

A. No.

Q. In the concept of the Pharmacopeia, are such drugs official regardless of their intended use?

A. No. We have to restrict the word "official" to the articles [269] when they are intended for use as medicine.

A good example is sugar, sucrose, which is used in medicines, and when so used is an official U.S.P. article, but when it appears in the grocery store for use in coffee it certainly is not an U.S.P. official article.

Q. Do you have any other such examples in mind?

A. Oh, sodium chloride is one. Salt. Plain salt.

Q. Are you familiar with the substance phenolphthalein?

A. Yes. That is a fairly well-known laxative substance. It is sold in considerable volume by one well-known Michigan pharmaceutical house under the trade name Phenol Lax Wafers and, yet, it is also a very widely used chemical indicator, and, when so used, is certainly not a drug because it is simply to indicate whether a solution is acid or alkali.

The Court: Purely as a matter of curiosity, how are we getting over in the laxative field?

Mr. Williams: He was merely giving—

The Court (interposing): Or sugar on some grocery store shelf?

Mr. Williams: He was merely giving an example of a drug which was admitted to the Pharmacopeia, and which was, therefore, official, which might be used in a manner which would cause it not to be a drug for that use.

There has been some testimony about intended [270] use of substances and the effect of that intention or labeled use upon the status of the substance under discussion.

The Court: I thought that the express use of the disks that we are concerned with here has been pretty well established by all of the witnesses.

Mr. Williams: Well, I hope it has, your Honor.

The Court: The use it has been put to seems to be pretty well clarified, as far as I am concerned.

Mr. Williams: If it is clear to your Honor and you are satisfied that there is adequate evidence with respect to whether a substance which is a drug in some context is not a drug in other contexts, then we are perfectly willing to drop this subject.

The Court: I presume that somewhere along the line this witness is going to have something to say about the matter that is here for discussion.

Mr. Williams: That's correct.

The Court: It would be rather unusual if you brought him here and he did not have some intention to do that, and that is all I am interested in here, is this one.

Mr. Williams: I think that the background would turn out to be useful, but if you prefer—

The Court (interposing): I don't question that. The publication that he has his roots in is mentioned in the [271] statute. I don't know how much more you need than that, as far as I am concerned.

Whether or not they are all in agreement is another thing. But Congress has seen fit to identify this publication as one that is official and can be used in the interpretation of the intent of the statute, I think.

Mr. Williams: Your Honor, I am attempting to show here—one aspect of my effort is to show that only certain kinds of substances are listed in the Pharmacopeia, and by "listed" is meant listed in the monograph or admitted to the monograph; that substances other than that kind

are not admissible; that under the definition of "drug" in the statute we have two clauses which are here pertinent. The first is articles recognized in the official compendia, of which the U.S.P. is one. The second is articles used in the diagnosis, cure, mitigation, treatment, prevention of disease.

One of my contentions, if you will recall, is that the first clause referring to the Pharmacopeia and other compendia refers to specific articles, namely, those listed in the compendia as drugs in the monograph and those which are eligible for admission.

The second clause is restricted to the type which are admissible to the compendia.

Therefore, I have perhaps over-emphasized the [272] status of the various types of substances which are named in the compendia. Those in the monographs which are official drugs, they are the only official drugs; they are the only ones recognized by the compendia as the type which are referred to in the statute.

All the others, the hundreds of reagents listed in the back of the book, may or may not be drugs.

The Court: Well, I don't think it makes a great deal of difference, so far as I am concerned, what your thoughts are on the matter—and I don't want to be abrupt about this. I am only interested in the testimony of the witnesses and these experts as it relates to the problem I have here for determination.

I formed the opinion a long while ago that if any of these antibiotics are liquids, and if they will clean windows, in that capacity, it isn't a drug.

It is not that difficult. As far as I am concerned, it can be the only other commercial use.

Mr. Williams: I was trying to relate it, your Honor, but I will proceed to the disks.

The Court: That is what I am interested in principally.

Q. (By Mr. Williams, continuing): Dr. Miller, are you familiar with the use of sensit.vity disks?

[273] A. Yes, in a general way.

Q. From what source did you derive your familiarity?

A. From the general publications. I have seen them. I

have used things like disks prior to the time they ever came on the market. As early as 1943.

Q. Are sensitivity disks listed in the monograph section of Pharmacopeia?

A. No.

Q. Are they listed anywhere in the Pharmacopeia?

A. No.

Q. Have they been formally proposed for listing in the Pharmacopeia?

A. Yes.

Q. They have been?

A. They have been, but the decision was that they were not—

Mr. Franchino (interposing): Objection, your Honor, as to reasons why disks may or may not be included in the Pharmacopeia.

The Court: He has, in my opinion, identified himself as being connected with this publication and apparently in charge of the publication, or seeing that the publication gets out on time; and, if he knows the reason why it hasn't been, I would think that would be competent.

Again you have a publication that is mentioned [274] by Congress as part of this statute. So, if there is any ambiguity about it, why, let's get it out in the open.

Mr. Franchino: Our general reason is that there is no ambiguity, that the U.S.P. speaks for itself, and the disks, we concede, are not mentioned in it.

The Court: Then it might be helpful why they are not mentioned in it. It would be to me, at least.

Mr. Franchino: Thank you, sir.

The Court: This may speak for itself, but it is going to have an awful lot of talking to do before I am going to comprehend it. This is one of the books I am not going to take home and read. I have no background in drugs, other than the drugs that I might use occasionally.

Mr. Williams: Do you wish to have the question read?

The Witness: I think it would be better.

Mr. Williams: Mr. Reporter, will you please read it.

The Reporter (reading):

"Q. Are sensitivity disks listed in the monograph section of Pharmacopeia?

A. No.

Q. Are they listed any where in the Pharmocopeia?

[275] A. No.

Q. Have they been formally proposed for listing in the Pharmocopeia?

A. Yes.

Q. They have been?

A. They have been, but the decision was that they were not"—

A. (Continuing): —they were not considered to be drugs.

Q. (By Mr. Williams, continuing): Is the fact that disks may bear an antibiotic of any significance in connection with the question of their admissibility to the monograph section as drugs?

A. May I—I want to be sure I understand. The question is, does the fact that the antibiotic disk contains antibotics have a bearing on whether they would be admitted to the Pharmacopeia?

Q. Yes.

A. No. No, it didn't. It was a question of their use that determined whether or not they would be in the Pharmacopeia.

Q. If, perchance, disks should be named in the Pharmacopeia, would they be put in the monograph section?

A. No, I wouldn't expect they would be. They would appear in the section under clinical adjuncts where we already have agents that are used for testing specimens taken from the [276] body, but the agents are not used on the person of a patient.

The Court: They would be placed in what category?

A. In the category of "clinical adjuncts" along with typing serum, blood-typing serum.

Q. (By Mr. Williams, continuing): Are clinical adjuncts drugs?

A. No.

Mr. Williams: Thank you, Dr. Miller.

Cross Examination

By Mr. Franchino:

Q. Good morning, Dr. Miller.

A. Good morning.

Q. Now, the U.S.P., Dr. Miller, which is the volume that we are talking about—if I mention "U.S.P." I am talking about the book, although I will try to say "Pharmacopeia."

A. We use the two terms interchangeably.

Q. Good. You stated that clinical adjuncts are not drugs; is that correct?

A. That is the view of the U.S.P. Committee on Revision.

Q. Now, clinical adjuncts are found in the back of the U.S.P.?

A. Yes.

Q. In the non-monograph section; is that right?

A. Yes.

* * * *

[286] Q. Would you turn to Page 845 of the U.S.P., Dr. Miller. I wonder if you would read for me the first three sentences that appeal in the first paragraph under the heading, "Adjuncts and Clinical Reagents"?

A. Yes. (Reading)

> "Pharmacopeial standards are provided in this section for several adjuncts and reagents used in medicine which, although not used on the person of the patient, are of such nature as to be closely associated with drugs so used. This common attribute constitutes a basis for bringing together the U.S.P. standards on these agents. The standards have the same force and effect as those of the monographs section."

Q. Thank you, sir.

The Court: I think, for the purpose of the record, you might as well read the rest of it.

A. The rest of the section?

[287] The Court: Yes. On "Adjuncts and Clinical Reagents."

A. (Continuing reading):

"They are appropriate for articles prepared for the following purposes: Absorbable Dusting Powder—as surgeon's glove lubricant; Blood Grouping and Typing Serums—for typing the blood of donors and recipients prior to transfusions; Carbon Dioxide Absorbants—for removal of carbon dioxide from air that is re-breathed; Filtering Media—as aides in pharmaceutical filtration; and Thromboplastin—as an aid in determining clotting time of blood."

That is the entire section.

Q. (By Mr. Franchino, continuing): So that disks, sensitivity disks are put in that "Adjuncts and Clinical Reagents" category, as you suggested that they would more logically fit into?

A. Yes.

Q. The standards that would pertain to sensitivity disks would have the same force and effect as those of the monograph section within the meaning of this paragraph; is that correct?

A. We would say so. But perhaps it isn't for the U.S.P. Committee on Revision to say what force they have. It might be regarded as a pious hope.

As you know, the Pharmacopeia standards have force only to the extent that the Food & Drug Administration [288] enforces it. We are not a police agency. We simply provide these standards as—it has been often said—as an extension of the legislative arm of our government. We have no power to enforce.

So we put them out. We say we believe they are respectable; we would like to have them useful. But their force—whatever force they have—would be up to the F.D.A.

Q. In other words, it would be up to the intent of the Congress?

A. Yes.

Q. And the Government, and not up to the intent of the U.S.P. Committee?

A. No. You are reading something in there I did not intend.

Not the intent of Congress, because Congress has delegated to the U.S.P. to provide standards, and we, in putting them in there, if we applied them to disks we would be endeavoring to comply with the intent of Congress.

But the force they would have actually would have to be determined by the—whoever it is that does enforce them.

Q. Would you characterize them as a self-serving statement?

A. I suppose it is in your definition. I am not used to using that phrase.

The Court: At this point I would be interested [289] if you know and can give the answer if you or any of your associates—either present associates or any past associates that might have been connected with the publication—were called in to give testimony before Congress in relation to the Act we are concerned with here, or any of the amendments to it?

A. Yes, I am sure that the record shows that.

As a matter of fact, I might say that I was consulted by Senator Byrd just last week, or I sent in a letter just last week in response to a request from him in respect to the reference to the U.S.P. in the new Medicare Bill. That is the most recent consultation that we have had from Congress.

I have appeared before committees of both the House and of the Senate, the Kefauver Committee and the Harris Committee, in respect to the 1962 Amendment.

So that over the years there has been such consultation by Congress with our committee members, and I might say a number of our committee members, members on the Board of Trustees, have appeared before committees of Congress.

The Court: When any members, or any of your associates, appeared before Congress, or a committee, has there ever been a discussion about these disks?

A. No.

* * * *

[290] A. Do you mean, do we feel free to use F.D.A. methods in drafting [291] our standards?

Q. Yes.

A. The answer would be "Yes." We receive many helpful suggestions from F.D.A. They are one of our most successful sources of help, I am glad to say.

Q. Have you had a chance to examine the antibiotic disk certification standards that F.D.A. has promulgated and published in the Federal Register?

A. I have a general understanding of them. I receive them. They are quite voluminous, as you well know. I don't have time to read them through completely.

Q. In the event disks would be included somewhere in the U.S.P., I presume there certainly would be standards for that?

A. Yes.

Q. If this were the case—

The Court (Interposing): Well, we are back in the same field you objected to in relation to Mr. Williams' questions.

Mr. Franchino: No. You see—

The Court (Interposing): Talking about some future publication. And I sustained that objection. So you are right in the same field.

Mr. Franchino: I haven't heard any objection, your Honor.

[292] The Court: Well, you heard one from the Court. And I am directing the conduct of the trial.

What I am trying to do is remind you that you are going into something that sounds to me as though you are in the same field that I stopped the other side from going into.

Mr. Franchino: It is well-taken, sir. Thank you.

I have no further cross-examination, your Honor.

The Court: Any re-direct?

Mr. Williams: Yes. Thank you.

Re-direct Examination

By Mr. Williams:

Q. Will you refer again to page 845 of the U.S.P., that portion under the heading, "Adjuncts and Clinical Reagents," about which Mr. Franchino talked to you?

A. Yes, I have it.

Q. Were these substances listed there ever included in the monograph section of U.S.P., or any of them?

A. Yes. Some of them were.

Q. Which ones?

A. The blood grouping serums were. Soda lime, which is listed [293] on page 848, was in the monograph section at one time.

The purified siliceous earth; which is on 849, was one time.

And at the moment I can't say for sure whether thromboplastin was or not.

Q. Why were they removed from the monograph section and put in the back?

A. For the reason they are not used in or on the person of the patient. They are a different kind of an article. And we had enough reservation within the Committee on Revision that—the sub-committee that makes the selection as to whether they belonged in the Pharmacopeia at all or not, that although they had been in, the ones I have mentioned, standards for them were needed and they were retained in this section apart from the monograph section in order that standards would be provided.

Q. Is your explanation related to the clause in the first sentence under the heading "Adjuncts and Clinical Reagents," which reads, "although not used on the person of the patient"?

A. Yes. Yes. That is what I have in mind.

The Court: What page is that on?

Mr. Williams: 845, your Honor.

The Court: No. I mean "although not used."

Mr. Williams: It is the first sentence under [294] the heading "Adjuncts and Clinical Reagents" on page 845. The explanation of why they are here.

The Court: Yes. All right.

Q. (By Mr. Williams): And is that related to their status or lack of status as drugs?

A. Yes. Within the Committee's view and my own view.

Q. That they are or are not?

A. Oh, they are not drugs, because they are not used on the person of the patient; they are used on a specimen taken from the patient.

Q. Now, do you consider the testimony you have just given as consistent with the statement in the same location on the same page, "The standards have the same force and effect as those of the monographs section"?

A. That probably is what Mr. Franchino would classify as a "self-serving statement." I think I called it a "pious hope."

Q. Mr. Franchino talked with you about whether disks, were they named in the Pharmacopeia at all, would be listed in one part or another part. We talked earlier about the use of the term "listed" and "admitted," and their meaning.

Now, would you tell us again what "listed" in the Pharmacopeia or "admitted" to the Pharmacopeia means to the Admissions Committee and to you? I mean Committee on Revision and you.

[295] A. We use the word "admitted" and "recognized" as being interchangable. We don't often use the word "listed."

But in order to have some way of distinguishing things that are mentioned, that are not admitted or recognized, I generally use the word "listed" or sometimes the word "named." But "listed" is a very convenient way—a term to apply to those that are mentioned in the back of the book without being admitted.

Q. There was a reference by Mr. Franchino to presence in the monograph section of orange oil, lemon oil, and such substances, which don't sound very much like drugs. Are those substances included because they are drugs in their own right or because they are components or used as components in substances?

A. Because they are used as components of articles that are used for medicinal purposes.

Q. Do you include in the monograph section any substance as a diagnostic agent which is not used in the patient or applied to them?

A. I don't think we do. I don't know a single example.

Mr. Williams: That is all, your Honor. Thank you.

The Court: Any re-cross?

Mr. Franchino: Yes, sir. One or two questions, your Honor please.

* * * *

[297] Mr. Williams: I will call Dr. Feldmann.

DR. EDWARD G. FELDMANN was thereupon called as a witness on behalf of the Claimant and, having been first duly sworn, testified as follows:

Direct Examination

By Mr. Williams:

Q. Dr. Feldmann, will you state your name and address?

A. My name is Edward G. Feldmann. My office address is 2215 Constitution Avenue, Northwest, Washington, D.C.

Q. What is your present occupation and position, Dr. Feldmann?

A. I am, by occupation, a pharmaceutical chemist. My primary position is Director of Revision of the National Formulary.

In this capacity I have several other responsibilities, which include the following:

Chairman of the Committee on National Formulary;

Director of Revision of National Formulary;

Director of the Scientific Revision of the American Pharmaceutical Association;

And Editor of the Journal of Pharmaceutical Sciences.

Q. Will you give us a sketch of your educational background, please, Dr. Feldmann?

[298] A. I received my Bachelor of Science Degree in Chemistry from Loyola University in Chicago.

Q. Loyola?

A. Loyola University in Chicago. Master of Science in Pharmacy Degree from the University of Wisconsin;

A. Ph.D., a Major in Pharmaceutical Chemistry and Minor in Biochemistry from the University of Wisconsin.

I have had some postgraduate, postdoctorate courses at the University of Chicago and Northwestern University.

Q. And after you finished this elaborate education, what did you do?

A. I was associated with the American Dental Association in Chicago as Senior Chemist with the Council on Dental Therapeutics, and subsequently assumed the position of Director of the Division of Chemistry of the American Dental Association.

My association with the American Dental Association extended from 1955 to 1959. I then became associated with the American Pharmaceutical Association in 1959, and succeeded to my present position in 1960.

Q. Have you written for the scientific literature in your field?

A. Yes, I have. I have published approximately twenty-five to thirty original research publications, and possibly an equal number of other professional articles relating to matter [299] of drug standardization and related subjects.

Q. What is the National Formulary?

A. The National Formulary is a compendium of drugs and drug standards. The drug standards are specifications, tests, and assays intended to provide information for the identity, purity, quality, and strength of the articles admitted thereto and described therein.

Q. Have you told us by whom the National Formulary is published?

A. No, I have not. The National Formulary is published by the American Pharmaceutical Association.

The first National Formulary was published in 1888. It has been revised at regular intervals since that date. It is published by the American Pharmaceutical Association under the auspices—no. The responsibility for the—the direct responsibility for the revision of the book is assigned to the Committee on National Formulary. The Committee on National Formulary, in turn, operates under the direct responsibility and authority of the Council of the American Pharmaceutical Association, which is the governing body of the American Pharmaceutical Association.

Q. What is the American Pharmaceutical Association?

A. The American Pharmaceutical Association is the national professional society of pharmacists in the United States.

Q. Will you state in a little more detail what the basic purpose [300] of the National Formulary is?

A. The National Formulary has as its basic purpose the promulgation of standards relating to drugs for the benefit of the professions of Pharmacy, Medicine, and the general public.

As a result of the recognition accorded to the National Formulary by the Federal and State laws, the National Formulary has come to have also as its main purpose the establishment of standards which are suitable for enforcement purposes as they relate to the drugs described therein.

Q. In general, how are articles selected for listing in the monograph section of the National Formulary?

Before you answer that, Dr. Feldmann, give us a brief statement of the several principal divisions of the Formulary.

A. The principal divisions of the Formulary are the General Notices section, which provides the information regarding interpretations of the information included in the book.

This is followed by the Monograph Section, which is the principal portion of the book, and in the Monograph Section the individual drugs which have been admitted to N.F. are detailed, and the tests—related information pertaining to them are given in detail.

Following the Monograph Section, there is the General Test section, which includes detailed procedures which [301] are referred to in many monographs for the sake of avoiding unnecessary repetition in all of the monographs.

The General Test Section permits reference to it.

This is followed by the Reagents Section, which provides information pertaining to the purity required of reagents used in National Formulary tests.

This is followed by the General Information Section, which is a section of, as the name implies, simply general information, various appendices, addenda, and so forth.

I believe that covers it.

The Court: We will take a recess at this time.

(A recess was thereupon taken.)

The Court: All right.

Mr. Williams: Will the Reporter please read the last question and answer of the witness?

(The record was thereupon read by the Reporter.)

Mr. Williams: Thank you.

Q. (By Mr. Williams, continuing): Doctor, what are the criteria for listing of articles or substances in the monograph section of the National Formulary?

A. In a sense, there are two general criteria, the first being that the articles are such that they are intended for [302] administration to, or use on the patient.

The second criterion is that the articles have therapeutic value or are used as excipients in articles—dosage forms—having therapeutic value.

The Court: Will you give an explanation of "excipient"?

Q. (By Mr. Williams, continuing): Can you explain the word "excipient"?

A. The word "excipient" as I used it here would refer to substances incorporated into a pharmaceutical dosage form to facilitate in the administration of the active ingredient to the patient.

If I may cite a couple of examples:

In administering a drug by injection, the water that is used to dissolve the drug would be an excipient.

In giving a drug by tablet dosage form, the lubricants, binders, which are utilized in forming that tablet would be excipients.

In the case of ointments of solution dosage forms, items such as flavoring agents, suspending agents, solvents, other such articles would be excipients.

Q. Are any articles admitted to the monograph section of the National Formulary which are not drugs, as that term is understood by the Revision Committee?

[303] A. I would hope not. Not to my knowledge.

Q. Is that the policy?

A. Yes, it is the policy.

Q. In this process of selection, what is your function, Dr. Feldmann?

A. My personal function?

Q. In the process of selection of substances for admission to the monograph section?

A. First of all, my general capacity is such that I would supervise and see to the administrative functioning of the various different committees which have responsibility for selecting the drugs to be admitted, or developing the monographs, the standards, specifications for those drugs, and then ultimately the publication of the book.

With regard to the specific matter of the selections, I serve as an ex officio member of the N. F. Advisory Committee on Admissions, which is the group which specifically reviews drugs available, for the selection of those to be admitted to the new edition of the Formulary.

Q. Do you participate in the decisions on admissions of drugs?

A. Yes, I do.

Q. Dr. Feldmann, I will ask you to read the paragraph under the heading "General Notices" on page 1,—that is Arabic 1—of the National Formulary, entitled "Official." (handing book [304] to the witness.)

A. Do you wish me to read the entire paragraph?

Q. Yes.

A. (Reading):

> "The word 'official' as used in this National Formulary or with reference hereto, is synonymous with 'National Formulary' and with 'pharmacopeial.' The standards apply equally to articles bearing the official titles, or synonyms listed under the official titles, or names derived by transposition of the definitive words of an official title. Articles listed herein are official and the standards set forth in the monographs apply to them only when the articles are intended or labeled for medicinal use and when bought, sold, or dispensed for this purpose, or when used in the tests and assays herein provided."

Q. That portion which you read which referred to articles listed herein as being official, to what listing does that term "listed herein" refer?

A. It refers to the monographs or the articles in the monograph section, but I might refer to the page XXIII where the heading of a complete list of the admissions—the articles admitted to the monograph section—is given, and the word "listed" as used in that general notice statement would be synonymous with the word "list" as it appears at the head of this [305] tabulation.

In other words, it is the articles in the monograph section.

Q. Did you say that in there it also uses the term "admitted"?

A. Yes.

Q. What does "admitted" mean? Admitted to what?

A. To the monograph section. The words "admitted," "recognized," "official," are synonymous with the way we are using—or referring to the word "listed" here. In other words, those articles which appear in the monograph section.

Q. Are substances other than the monograph articles named in the National Formulary? Are there any such substances?

A. Yes, there are.

Q. And what are they?

A. Some of the substances would be those which appear in the reagents section, which provide specific information regarding the purity of the articles used as reagents in testing inert drugs.

Q. Are these reagents official drugs?

A. No, they are not.

Q. In the sense of the N.F. usage, are articles listed in the monograph section considered to be official for all the uses to which they are put?

A. No. I think, as the statement which I read indicates, they [306] are official only when labeled or intended for medicinal use, or bought, sold, or dispensed for that purpose.

Q. Is the term "recognized" used in the National Formulary?

A. Yes, it is.

Q. Can you point to the page and place where it is used?

A. I believe it appears in a number of places. I am immediately familiar with several places on page 6.

Would you like me to read the pertinent sentence?

Q. Yes. Just enough to convey the meaning.

A. On page 6, in one place it reads—this is under "Category," the first column on page 6:

(Reading):

> "A statement of Category usually is provided in each monograph as useful information. It indicates the therapeutic or pharmaceutical basis for recognition in the National Formulary and generally represents an application of the best known pharmacologic action of the article or of its active ingredient."

And the following paragraph, the first sentence reads.

(Reading):

> "The Usual Dose generally given in the monograph is that which may be expected [307] ordinarily to produce in adults, following oral administration unless otherwise specified, the therapeutic effect for which the article is recognized."

Q. In the N.F. sense, what articles named in the Formulary are recognized?

A. Those which appear in the monograph section.

Q. Do you know what a sensitivity disk is?

A. I am generally familiar with them; yes, sir.

Q. On what basis—from what do you derive your familiarity?

A. General background in bacteriology, which included a graduate course work and research, and my viewing the use of such disks, in addition to reading of the literature, scientific literature, pertaining to them.

Q. Do you have any familiarity with the procedure of sensitivity testing by the use of the disk?

A. Yes.

Q. Have sensitivity disks ever been considered for listing or naming in any part of the National Formulary?

A. There has been some general consideration given

to this. A general suggestion made that they might be considered.

Q. Are they the kind of substances which, under N.F. policy would be considered for listing in the monograph section?

A. No, they are not.

[308] Q. Why?

A. As indicated earlier under the criteria for admission, articles to be admitted to the monograph section would have to be administered—would be such that they would be administered to the patient for use on the person of the patient.

In view of the fact that antibiotic disks are not used in this, or intended to be used in this manner, they would not qualify for inclusion in the monograph section.

Q. Do you happen to know why a chemist was selected as Director of Revision of the National Formulary instead of a medical doctor?

A. I think the probable basis for this is the fact that the bulk of the content of the National Formulary—

Mr. Trumbauer (interposing): I am going to object to that, your Honor, before the witness goes any further. He was asked the question whether he knows, and he should answer that either he knows or he doesn't know. Either "Yes" or "No."

Mr. Williams: I will withdraw the question, your Honor.

The Court: All right. That takes care of it.

Q. (By Mr. Williams, continuing): Are there any antibiotic drugs recognized in the National Formulary; that is, do any of them [309] appear in the monographs?

A. Yes, indeed.

Q. Does that fact have any bearing, in the N.F. sense, on the question of whether, when those drugs, those antibiotics are put to a different use, as on sensitivity disks—

Mr. Franchino (interposing): Objection, your Honor.

Mr. Williams: Let me finish the question.

Q. (By Mr. Williams, continuing): If one of the antibiotics recognized in the monograph section were used on a sensitivity disk, would that have any bearing—that

fact have any bearing on the question of admissibility to the National Formulary of the disk?

Mr. Franchino: I will withdraw the objection as a result of rephrasing the question.

The Witness: May I ask that the question be repeated, please?

Mr. Williams: Would you read it, Mr. Reporter?

(The last question was thereupon read by the reporter.)

A. This would be irrelevant, because the fact that—the matter of whether or not the antibiotic substance as a drug is to be admitted to the National Formulary is completely another matter from other uses of that substance. Consequently, turning that [310] case around, as I gather you have put it, whether or not the antibiotic is in the National Formulary would be irrelevant to the consideration as to admission of the disk. And as I stated earlier, they are, per se, excluded because of their intended use; that they would not qualify for it.

Q. What is a reference standard, Dr. Feldmann?

A. A reference standard as intended or as understood by the National Formulary is a purified substance intended as a substance of reference in performing various chemical and biological test procedures.

We have what are known as N.F.—or National Formulary—reference standards. These reference standards are articles, or chemical substances, which have been highly purified, prepared, and which are tested, standardized, packaged, and distributed through the National Formulary offices on a self-sustaining program for use by laboratories wishing to run various assays or test procedures described in the National Formulary.

Q. Are these reference standards which are listed in the National Formulary official drugs in the sense of the Formulary?

A. No, they are not, although many of them do have the same titles as the monograph articles.

In other words, we have a monograph for a certain particular article, certain drug. We may have a [311] National Formulary reference standard, which is a N.F.

reference standard, for that article. That reference standard, however, is not a drug because it is not intended for use as a drug. It is intended solely for use in the procedures, the test procedures described in the National Formulary monograph section.

Q. Do you have in the National Formulary any antibiotic reference standards?

A. In the National Formulary, we do.

Mr. Williams: That is all.

Cross Examination

By Mr. Franchino:

Q. Dr. Feldmann, is there a third compendium in addition to the N.F. and the U.S.P. that is sometimes looked to for information regarding drugs?

A. You mean is there a third official compendium recognized by the law?

Q. Yes.

A. Yes, there is.

Q. What is the name of that one?

A. The Homeopathic Pharmacopeia of the United States.

Q. Now, the NF does not purport to include every item or article that is known to medicine and science to be a drug, [312] does it?

A. No, it does not.

Q. And, to the best of your knowledge, neither does the U.S.P.?

A. No. To the best of my knowledge, it does not.

Q. And, to the best of your knowledge, neither does the Homeopathic Pharmacopeia?

A. That is correct.

Q. And, as a matter of fact, all three compendia taken together don't purport to include every item or article that is known as a drug to science and medicine?

A. No. We purport to consider for admission all drugs which have reputed therapeutic value.

Q. When you say "we," are you talking about the N.F. or all three put together?

A. I speak specifically for the N.F. and my understanding, at least, of the U.S.P., but not for the Homeopathic Pharmacopeia.

Q. Now, as I understand by your criteria for inclusion in the N.F., a product must be one intended for administration to or use on patients; and, secondly, must have therapeutic value; or must be used as an excipient or excipients in articles having therapeutic value or use; is that correct?

A. Yes.

Q. Suppose a product is held out, or represented, or claimed to have therapeutic use, does this representation or holding-out—[313] is this sufficient to entitle the article to consideration for inclusion in the N.F.?

A. It would be sufficient to consider that article for inclusion, yes.

Q. Would such an article—that is, an article that is claimed to have efficacy, but indeed or in fact, has none—would such an article actually be listed in the N.F.?

A. If, in the opinion of our medical advisory panel, such an article which has reputed or professed therapeutic value, but in the opinion of this panel—and medical advisors—does not have, I wouldn't expect such an article to be admitted to the N.F.

Q. You stated that there were antibiotic reference standards incorporated into the N.F.

A. Yes, I did.

Q. Could you tell me if any of these were included as a result of reliance upon antibiotic standards that had been developed by the Food & Drug Administration?

The Witness: May I ask that that question be repeated, please?

(The last question was thereupon read by the Reporter.)

A. The National Formulary utilizes many sources of information in developing the tests, assays, specifications, which are [314] embodied in it. Much of this information comes to us from sources, including the Food & Drug Administration.

I would expect, therefore, that information which was developed in Food & Drug Administration laboratories—perhaps published in the literature—was drawn upon in the development of certain of the National Formulary monographs pertaining to these antibiotic substances.

Furthermore, I do know as a fact that in developing reference standards it has been our practice to have several different laboratories test those reference standards. I do not believe it would be divulging a confidence here to indicate that the Food & Drug Administration Laboratories are one of the laboratories which has participated in collaborative studies resulting in the selection of the reference standard materials for the antibiotics.

Q. Is honey listed in the National Formulary as an excipient or as a drug? As an article that actually has therapeutic value?

A. Will you permit me to refresh my memory by reference to the book?

Q. Certainly.

The Court: He wants to look at the book. Go ahead.

A. (Examining book.) The monograph for honey, which appears on Pages 164 and 165 of the National Formulary, states in the monograph, "Category: Pharmaceutical necessity."

[315] This would indicate it is admitted for its value as a pharmaceutical excipient, as I just described or defined earlier in the course of my testimony. In other words, not as a therapeutically useful article—

Q. (Interposing): So that the—

A. (Continuing):—with therapeutic medicinal value.

Q. So that the "Category: Pharmaceutical necessity" applies to excipients, binders, and the like; is that right?

A. In general, yes. I would say in every instance that I can think of.

Q. Do you agree that as a medical and scientific proposition the term "drug" means many things to many people?

A. I think I would have to say "Yes," if you are including everyone, including the layman. Anyone to whom

—

Q. (Interposing): Do you agree as a medical and scientific proposition the term "drug" may mean different things to different scientists and physicians?

A. I would guess that this is the case. If I may be permitted to add to that last answer—

Q. (Interposing): Certainly.

A. (Continuing):—I think that different people would define it using slightly different phraseology or words. I think that the concept is relatively standardized, however.

Mr. Franchino: I have no further questions.

[316] The Court: Do you think that the fact that "drugs" mean many things to many people, including lay people, that that is the reason why Congress designated these three publications as the official source of identification for drugs?

A. Well, your Honor, I think that this points out the need for a specific definition of what a drug is.

The Court: You mean the fact that drugs mean many things to many people?

A. The term "drug" meaning different things to different people, I would assume was the basis for Congress setting down a definition of what constitutes a drug.

The Court: All right.

Re-direct Examination

By Mr. Williams:

Q. Dr. Feldmann, since your opinion is being asked as to what a drug is, do you consider that the terms describing a drug which are followed or used in admissions to the National Formulary are a sound definition of a drug? You described the terms under which articles were admitted.

The Court: What sort of an answer do you expect to that one?

Mr. Williams: I expect him to say "Yes."

[317] The Court: It would be unusual if he said anything else.

The Witness: Am I permitted to answer?

The Court: Why, sure.

A. If I understand the question correctly, you have asked me if the policies or guidelines used by the National Formulary in considering for admission articles into the National Formulary monograph section, whether that policy would be a sound basis for a definition of the word "drugs," and my answer to that would be "Yes."

Mr. Williams: That is all, your Honor.

The Court: Any re-cross examination?

Mr. Franchino: Just one thing.

Re-cross Examination

By Mr. Franchino:

Q. I wonder if you could name a drug for me in which honey is a pharmaceutical necessity?

A. There are certain cough medicines, cough syrups, in which there are various adjuncts, excipients, present. I believe that this is one of the primary uses of honey, as an excipient in flavoring cough syrups, making them more palatable, and therefore much more suitable for administration to the patient.

Q. It has no therapeutic merit in itself?

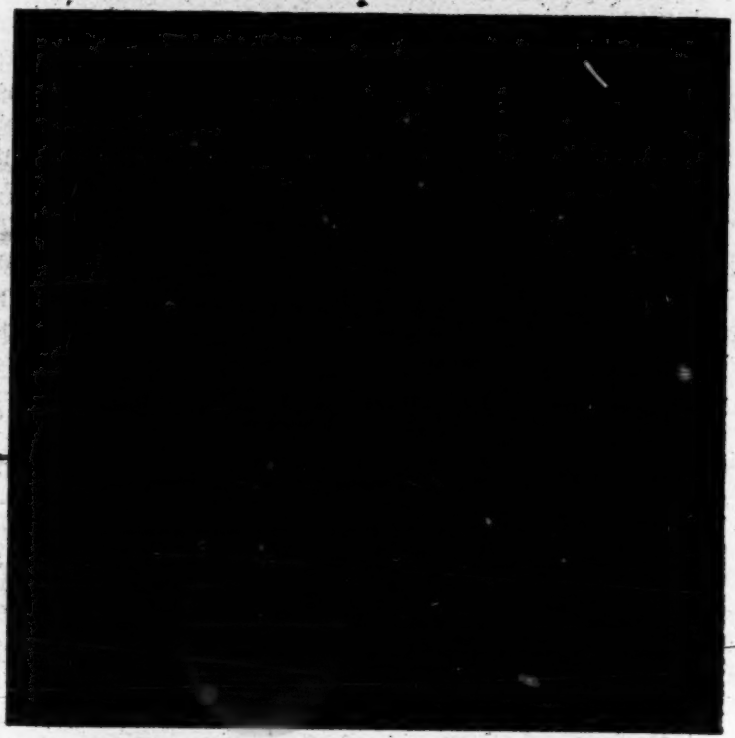
[318] A. It is not recognized in the National Formulary for any specific therapeutic merit.

* * * *

Libelant's Exhibit 1

LIBELANT'S EXHIBIT 1

[Bacto-Unidisk]



Libelant's Exhibit 1

[Label on side of carton of Bacto-Unidisks]

BACTO-UNIDISK

for

ANTIBIOTICS-SULFONAMIDES A-S#1

LOW CONCENTRATION

Code 7011 50 Unidisks

[Label on front of carton of Bacto-Unidisks]

Code 7011 50 Unidisks

BACTO-UNIDISK

for

ANTIBIOTICS-SULFONAMIDES A-S#1

LOW CONCENTRATION

AUREOMYCIN® Chlortetracycline	5 mcg.	STREPTOMYCIN	2 mcg.
CHLOROMYCETIN® Chloranphencol	5 mcg.	TERRAMYCIN® Oxytetracycline	5 mcg.
ERYTHROMYCIN	2 mcg.	TETRACYCLINE	5 mcg.
PENICILLIN	2 units	SULFADIAZINE	50 mcg.

for LABORATORY USE

Use with Bacto-Mueller Hinton Medium,
with or without added blood.

Keep in refrigerator at 2° c. to 10° c. for maximum strength

DIFCO LABORATORIES • Detroit 1 Michigan

Libelant's Exhibit 1

[Printed enclosure inside carton of Bacto-Unidisks]

Sensitivity Testing
Bacto-Sensitivity Disks and Bacto-Unidisks

Bacto-Sensitivity Disks and Bacto-Unidisks are standardized paper disks containing known amounts of the more commonly employed antibiotics, sulfonamides and other therapeutic agents. They are recommended as a rapid, practical, clinically accurate and inexpensive means of determining the relative sensitivity of microorganisms to these therapeutic agents. Bacto-Sensitivity Disks are especially valuable in selecting the drug effective against chronic or persistent infections refractory to primary therapy.

Bacto-Sensitivity Disks are available in 3 concentrations as ¼" paper disks; color coded to clearly identify and distinguish the therapeutic agent; packaged 50 disks per vial.

Bacto-Unidisks, employing the same methods of designation of the therapeutic agents, and the same concentration as employed by Bacto-Sensitivity Disks, are prepared under carefully controlled conditions insuring the uniform impregnation of eight standardized amounts of the microbial agents on uniformly spaced disks integrated as a unit.

Bacto-Unidisks are 35 mm. in diameter, ideally suited for the standard-sized Petri dish. The transfer of a single Bacto-Unidisk to an inoculated plate will demonstrate sensitivity of the micro-organism to the various chemotherapeutic agents incorporated in the unit. Bacto-Sensitivity Disks, containing agents other than those in the Unidisk, may be placed in the center of the plate for additional information.

Culture Media

Bacto-Heart Infusion Agar or Bacto-Tryptose Blood Agar Base, with or without added blood, is recommended for sensitivity testing with Antibiotics. These media contain p-aminobenzoic acid and other sulfonamide inhibitors and should not be used with Bacto-Sensitivity Disks or Bacto-Unidisks containing sulfonamides.

Bacto-Mueller Hinton Medium, with or without added blood, is recommended for all Bacto-Sensitivity Disks or Bacto-Unidisks containing sulfonamides. The use of me-

dia containing p-aminobenzoic acid or other sulfonamide inhibitors will inactivate the sulfonamide in the disk upon contact, giving an erroneous sensitivity test. Bacto-Mueller Hinton Medium, with or without added blood, is free from all sulfonamide inhibitors and must be used in sulfonamide sensitivity tests. This medium serves equally well in antibiotic sensitivity testing.

Peizer TB Medium prepared with Bacto-Peizer TB Medium Base and Bacto-Peizer TB Medium Enrichment is recommended for sensitivity determinations of tubercle bacilli.

Performance of the Test

Organisms other than tubercle bacilli

Plates of Bacto-Heart Infusion Agar, Bacto-Tryptose Blood Agar Base or Bacto-Mueller Hinton Medium, with or without blood, are inoculated either by smearing or streaking so as to obtain a heavy or confluent growth. Pure cultures or clinic specimens may be used as inoculum.

Staphylococci, especially resistant penicillinase producing, require a heavy inoculum to give a confluent growth for accurate sensitivity determination by the disk plate technique. Tests showing small zones of inhibition (12 mm. or less) around penicillin disks on light inoculations of Staphylococci should be repeated using a heavy inoculum to give confluent growth.

A diluted culture should be employed especially when testing sensitivity of sulfonamides since many organisms produce these compounds. Purulent exudates and other clinical material may also contain sulfonamide inhibitors and must be diluted to avoid inactivation of the sulfonamide in the disk. One drop of an 18 hour Brain Heart Infusion culture may be diluted with 100 ml. of sterile saline. One drop of this dilution is used as the inoculum. Excessive moisture is to be avoided. Immediately after inoculation, aseptically place the Bacto-Unidisk on the inoculated medium. Incubate plates at 35-37 C overnight or until sufficient growth appears to permit detection of zones of inhibition.

Bacto-Sensitivity Disks are removed from the vials using a flamed tweezers. The disks are placed on the inoculated plate leaving 3 to 4 cm. between disks. Individual Sensitivity Disks (not more than four) may be placed in the center of a Unidisk to give information on additional agents.

Bacto-Unidisks are removed from the envelope by cutting the edge of the envelope below the seal with a scissors taking care not to cut the Unidisk. The Unidisk is then removed with a flamed tweezers and pressed to the medium to assure complete contact, permitting maximum diffusion of agents.

TUBERCLE BACILLI

Pure cultures of Mycobacterium tuberculosis or clinic specimens may be used as an inoculum. Specimens such as treated sputum, spinal fluid, urine, etc., should have a viable acid fast organisms content corresponding to a Gaffky III or IV[1] (1 to 3 acid fast organisms per oil immersion microscopic field) to obtain an even distribution of colonies on the plate.

The medium is prepared from Bacto-Peizer TB Medium Base[2] and Bacto-Peizer TB Medium Enrichment, poured into sterile plates and allowed to solidify. A heavy suspension of the inoculum is streaked or smeared over the surface of the medium. Excessive moisture is to be avoided. Immediately after inoculation and using aseptic technique, place Bacto-Sensitivity Disks or Bacto-Unidisks on the inoculated medium.

INTERPRETATION OF TEST

The results obtained with Bacto-Sensitivity Disks, as with other sensitivity tests similarly conducted, are of a qualitative rather than a quantitative nature. The many variables that enter into a test of this type, such as the size of the inoculum, type of growth of the organism, amount of inoculum on the plate, thickness of the medium, incubation conditions, diffusion rate of the therapeutic agent, and rate of deterioration of the therapeutic agent

[1] Mitth. a.d.k. Gandhtsarnet., 2:126:1884.

[2] Am. J. Clin. Path., 20:682:1950.

during incubation, preclude its precise quantitative nature. Sensitivities are to be determined by the presence and not by the size of the zone of inhibition around the disks.

It is stressed that the differences in the diameters of the zones of inhibition obtained with like concentrations of the various therapeutic agents do not necessarily indicate their relative therapeutic efficiency. The rate of diffusion of the various therapeutic agents from the disks and through the medium influence the diameter of the zone of inihibition.

Sensitivities to a given therapeutic agent should be reputed by observing zones of inhibition as follows:

Sensitive	—zone around all concentrations
Slightly Sensitive	—zone around higher concentration
Resistant	—no zone around any concentration

The sulfonamide sensitivity test should be read as soon as growth develops and zones of inhibition are discernible. Many organisms produce sulfonamide inhibiting substances and, as incubation continues, these may diffuse into the zone of inhibition, giving an erroneous result.

Occasionally one will observe a double zone of growth around a Sulfonamide Sensitivity Disk on the medium with or without blood. This results from too heavy an inoculation of an organism, producing abundant sulfonamide inhibiting substances on prolonged incubation. Continued incubation permits the gradual neutralization of the sulfonamide, thereby permitting growth within the original zone of inhibition. The original or largest zone of inhibition is considered as the significant zone.

Complete discussion of sensitivity testing by the Disk Plate technique available on request.

DIFCO LABORATORIES
DETROIT 1 MICH USA

1119 HTTTT N-UH
Printed in USA

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

Civil No. 22619

UNITED STATES OF AMERICA

vs.

An article of drug consisting of approximately 5 cases of 55 cartons each, each carton containing 50 clear plastic envelopes of an article labeled in part: (case) "C-6010 Code No. 7011 Control No. 455142 Lot No. 16517—Sterilon Corporation—Buffalo 11, N.Y." (carton) "Bacto-Disks 50 Unidisks—" (envelope) "Bacto Unidisk for Antibiotics Sulfonamides A-S #1 Low Conc. Tetra Streptomycin Aureo Penicillin Chlor S'Diazine Terra Erythro Code 7011" (package insert) "Sensitivity Testing"

MEMORANDUM OPINION

[Filed July 21, 1966]

When is a drug not a drug? When it is a part of a device or contrivance *not* for administration to man or animals, says the claimant. A drug is never "not a drug" says libelant—once a drug, always a drug. And this approximates the semantical conflict brought to a pinnacle by the conclusion of a trial before this Court, sitting without a jury.

A number of medical doctors testified as to the function performed by the libeled article and as to their understanding of the word "drug". Their testimony was not such as to compel a specific conclusion on the merits of this controversy, despite the fact that it was both interesting and enlightening.

The United States of America, libelant herein, filed a Libel of Information against the article, as per caption in the above title, seeking a decree of condemnation as to

it pursuant to the provisions of the Federal Food, Drug and Cosmetic Act (21 U.S.C.A. § 334). Paragraph 4 sets forth the basis for the libel. It reads as follows:

> "4. That the aforesaid article was misbranded when introduced into and while in interstate commerce within the meaning of the Federal Food, Drug and Cosmetic Act, 21 U.S.C.[A.] as follows:
>
> 352(1) in that article *purports to be and is represented as a drug* composed in part of penicillin, streptomycin, chloromycin, tetracycline, and aureomycin, and it is not from a batch with respect to which a certificate or release is in effect pursuant to 21 U.S.C. 357(a) and 357(c) and the article is not exempt from such requirements." (Emphasis supplied.)

Let us at the outset describe the article involved here. It is referred to as a sensitivity disk—the package bears the legend "Bacto-Unidisk for Antibiotic Sulfonamides A-S # 1 Low Conc. Code 7011." The disk itself is a circular piece of ½ inch wide cardboard, having a diameter of just under 3½ inches. It resembles a bracelet. At evenly spaced intervals are printed the following words: "Penicillin", "Chlor", "S'Diazine", "Terra", "Erythro", "Tetra", "Streptomycin", and "Aureo". Extending inwardly from the ring directly in front of each word is a small circular paper unit approximately ½ inch in diameter. Each such paper unit is impregnated with the chemical whose name appears closest to it on the ring. A Xerox reproduction of the article appears as an appendix hereto. Each such chemical is commonly used as an antibiotic drug, excepting sulphadiazine. The disk is referred to as a sensitivity unit. We will refer to each of the eight units as a sensitivity unit. The function of each sensitivity unit is to serve an an indication of the sensitivity or reaction of a specimen from a patient to the particular chemical contained in the sensitivity unit. The patient's specimen may be in the form of sputum, urine, throat swab, or other matter which has been withdrawn from

the body of the patient. The reaction of the specimen serves as a guide to a medical doctor in his determination of the choice of antibiotic to prescribe for the patient. Perhaps the specimen reaction will indicate that the chemical contained in one sensitivity unit is more effective than that in another. The testimony in this case was to the effect that frequently a doctor has a choice of several antibiotic drugs to prescribe, with no persuasive basis for selecting one or another. The information obtained from the sensitivity disk may serve as a guideline to a doctor in choosing among several drugs, for administration to a patient, which without such information would be equal choice-wise. The testimony was that the disk is not primarily used in determining *whether* or not to prescribe an antibiotic, or sulphadiazine, but rather to aid in the choice of *which* antibiotic, including sulphadiazine, may be preferable. It appears to the Court that the use of the sensitivity disk in obtaining information provides a short cut. We are all familiar with situations where a particular antibiotic has been prescribed for a patient, taken by or administered to such patient with unsatisfactory results, requiring the prescribing of a different antibiotic which proves to be effective. It would seem that the use of the information obtained from the disk sensitivity test provides a means for eliminating much of the trial and error approach on the patient by screening out the non-advisable antibiotics without experimentation on the patient himself. In other words, the disk sensitivity units may serve as sort of guinea pigs, instead of the patients.

Claimant here challenges the conclusion of the Commissioner of Food and Drugs that its sensitivity disks are certifiable antibiotic drugs. Claimant takes no issue with the language contained in 21 U.S.C.A. § 352(1), quoted above. It does, however, take issue with the libelant's construction of 21 U.S.C.A. § 321(g)(2). We quote below the language of said subsection which is contained in the Definitions section of the Federal Food, Drug and Cosmetic Act:

21 U.S.C.A., § 321(g)

> "(g) The term 'drug' means (1) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (2) *articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals;* and (3) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (4) articles intended for use as a component of any article specified in clause (1), (2), or (3) of this paragraph; but does not include devices or their components, parts or accessories." (Emphasis supplied.)

It is the position of libelant that subsection (2) of the above has direct application to the libeled article herein. It is the position of claimant that such a strained construction of subsection (2) is completely unwarranted and contrary to the intendment of the definition. This brings us back to our initial query as to when a drug is not to be considered a drug. When asked whether he considered that "sensitivity disks are drugs in the medical sense or the scientific sense," one medical doctor witness answered: "I would have to say that it is drug usage in a scientific sense." (Transcript, page 99) The same witness testified as follows in answering the following question: (Transcript, page 100)

> "Q. Are you saying any more than that the information derived from these sensitivity tests is used as a sort of guideline in treatment, for example?
>
> A. No. I think that would be a very fair statement. As a guideline. It helps the antibiotic choice to be given."

Again this witness, Dr. Charles K. Wolfe, Jr., gave the following answer to the question propounded: (Transcript, page 103)

> "Q. Let's see. Do you have an example of something which is not taken into the body or is not ap-

plied to the body which you consider medically as a drug?

A. I don't believe I can think of one offhand."

Counsel on each side of this controversy have presented able arguments, both orally and in brief form, as to their respective positions and contentions. When it comes right down to the determination which we must make, a literal reading of (g)(2) which defines "drug" as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" clearly has application to the article libeled herein. Our reluctance to make this finding and conclusion our holding is due to the fact that it appears to us to be ridiculous and contrary to common sense. We are all the more convinced of this in the light of the definition appearing in the paragraph immediately following (g), which reads as follows:

"(h) The term 'device' (except when used in paragraph (n) of this section and in sections 331(i), 343(f), 352(c), and 362(c) of this title) means instruments, apparatus, and contrivances, including their components, parts, and accessories, intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; or (2) to affect the structure or any function of the body of man or other animals."

We are not here called upon to decide if the disk is a device, but it appears to us that consideration of it in this category under (h) is far more appropriate than consideration of it as a drug within the purview of (g). In view of our conclusion that the libeled article does not come within the purview of the definition of "drug", (21 U.S.C.A. § 321(g)) we deem it unnecessary to discuss other arguments advanced during the trial of this cause relating to side aspects of the issue. We are persuaded that the legislative intent here should not be interpreted to include this sensitivity disk as a drug, despite the fact that drugs are contained in the article, for the reason that no part of this article is administered to man or

other animals, either internally or externally, and that its sole function is to provide medical doctors with information for use by them as guidelines.

Appropriate findings and conclusions may be submitted.

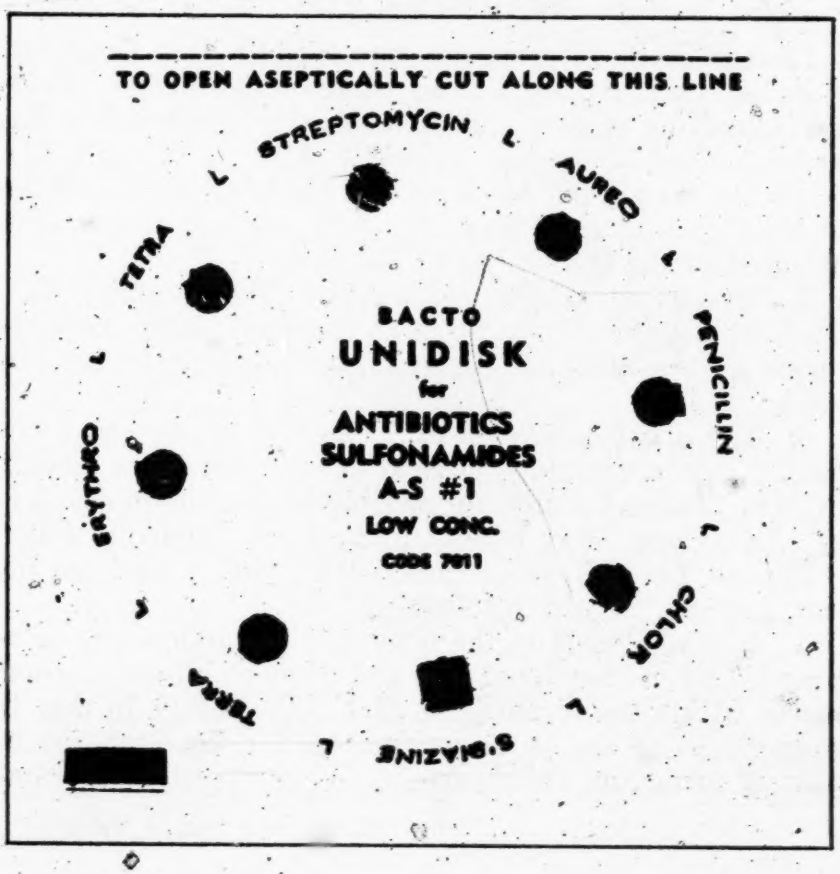
s/ Thomas P. Thornton
United States District Judge

July 21, 1966.

[Attached to Memorandum Opinion]

APPENDIX

Transparent Plastic Envelope Containing BACTO UNIDISK



UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

Civil No. 22619

UNITED STATES OF AMERICA

v.

AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * *

FINDINGS OF FACT AND CONCLUSIONS OF LAW.

[Filed August 21, 1966]

FINDINGS OF FACT

1. A libel of information was filed in this Court on May 25, 1962, by the United States (hereinafter "libelant") praying seizure and condemnation, pursuant to the Federal Food, Drug and Cosmetic Act (21 U.S.C. 334) of an article alleged to be an antibiotic drug. By order of the Court entered May 25, 1962, the said article was attached by the United States Marshal.

2. The seized article was shipped from Buffalo, New York by Sterilon Corporation to claimant, Difco Laboratories, in the State of Michigan, on or about March 20, 1962.

3. The article consisted of 5 cases of 55 cartons each, each carton containing 50 clear plastic envelopes labeled in part "Bacto-Unidisk for antibiotics Sulfonamides A-S # 1 Low Conc. Tetra Streptomycin Aureo Penicillin Chlor S'Diazine Terra Erythro Code 7011", with a package insert entitled "Sensitivity Testing".

4. It was alleged in the libel that the article was misbranded when introduced into and while in interstate commerce within the meaning of 21 U.S.C. 352(1) in that it purports to be and is represented as a drug composed in part of penicillin, streptomycin, Chloromycetin (chloram-

phenicol), tetrocycline, and Aureomycin (chlortetracycline), that it is not from a batch with respect to which a certificate or release is in effect pursuant to 21 U.S.C. 357 (a) and 357(c), and that the article is not exempt from such requirements.

5. Claimant, a corporation organized under the laws of the State of Michigan, filed a claim of ownership to the seized article and prayed to defend accordingly. Thereafter Claimant filed its answer and an amended answer.

6. Bacto-Unidisks, the brand name of the article seized, referred to generically as "sensitivity disks", are reagents used in laboratory testing of the sensitivity or resistance of microorganisms to chemicals corresponding to those with which the disks have been impregnated. The sensitivity disks in question are composed of eight paper units extending inward from a paper ring, each of seven of which is impregnated with a different chemical corresponding to a chemical commonly used as an antibiotic drug, and an eighth with a chemical (sulfadiazine) which corresponds to a chemical commonly used as a drug but which is not an antibiotic (Tr. 28-29, 87, 185-186, 239-240).

7. Preliminary to the sensitivity testing procedure a plated agar culture medium is inoculated with a specimen taken from the body of a patient (such as sputum, blood, urine), incubated for an 18-hour period, and then, after proper preparation, the suspect organism is placed on a slide and observed microscopically for identification. In the subsequent sensitivity testing procedure the organism so identified is isolated and transferred to an appropriate agar culture medium on a Petri plate, the sensitibity disk is placed upon the culture medium, and the plate containing the agar and the disk are incubated, usually for an additional 18 hours to permit the organism to grow. A "zone of inhibition" (an area in which the organism does not grow) around the disk indicates that the organism is sensitive to the chemical on the disk. The absence of a zone of inhibition indicates that the organism is resistant to the chemical (see Transcript references in Finding Number 6 and Tr. 33-35, 188).

8. The information obtained from the sensitivity testing procedure outlined in Finding Number 7 is used by the physician as a guideline to treatment of the patient (Tr. 29-30, 37, 40, 48-50, 94, 100, 107, 167, 191). The disk, the culture medium, the Petri plate, and the incubation are all a part of the testing procedure yielding this information. Such information could not be obtained from the disk itself. The test is only one of many sources (such as the physician's experience, clinical symptoms, the literature, and other tests such as urinalysis and blood serum tests) of the information upon which the physician relies in determining the treatment to be administered (Tr. 45-46, 53-54, 67-68, 108-110, 116-119, 145, 186-187, 240-241). The physician, frequently in emergency situations, selects and administers an antibiotic from the several (or "battery") usually available for the specific condition of the patient, without awaiting the results of the sensitivity test (Tr. 66-67, 88-89, 103-105). In such cases those results are then used by him to confirm his selection.

9. Sensitivity disks are not recognized in (admitted to) the United States Pharmacopeia or the National Formulary, which are "official compendia" under the Federal Food Drug and Cosmetic Act (21 U.S.C. 321(j), Tr. 273, 307), nor are such disks the kind of articles which are accepted for admission to the official compendia because, among other reasons, they are not regarded by the Committees on Revision (admission) of the compendia as drugs within the commonly accepted meaning of that term in medical science (Tr. 274-276, 301-302, 307-308, 317). In medical science those substances which are for administration to or for use on, a person for the treatment of disease or injury, are regarded as drugs (Tr. 102-103, 195, 199, 261-262, 283). This is the commonly accepted view of physicians generally. A physician who testified for libelant could think of no example of a substance not taken into or applied to the body which he would "consider medically" as a drug (Tr. 103).

10. The substances on the libeled disks are commonly used in other forms (tablets, ampules, etc.) in medical practice as drugs and are recognized as such in the official compendia (Tr. 308-309.) The libeled article, al-

though consisting in part of chemicals which are used as drugs when prepared in appropriate dosage forms for such use, is not intended to be used as a drug in the medical sense, since no part of it is to be administered to patients, either internally or externally. Similarly, the several substances with which the article is impregnated are not intended to be introduced into or applied to the human body when used on the disk.

11. The article does not purport to be and is not represented as a "drug" as that term is used in medical science or by physicians generally. It is labeled "For Laboratory Use" (Exhibit No. 1; Tr. 196-198).

Conclusions of Law

1. This Court has jurisdiction by virtue of 21 U.S.C. Section 334.

2. Only antibiotic drugs are subject to certification under 21 U.S.C. Section 357(a) and 357(c).

3. In medical science the concept of "drug" is limited to articles administered to man or other animals, either internally or externally. This is the generally accepted view among physicians (Finding Number 9). The evidence affords no basis for the conclusion that the definition of "drug" in the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321(g)) was intended by Congress to extend beyond the meaning of that term in medical science, to encompass these sensitivity disks. The definition of "drug" is found in 21 U.S.C. 321(g), which reads as follows:

> "The term 'drug' means (1) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (2) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (3) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (4) articles intended for use as a component of

any article specified in clause (1), (2), or (3) of this paragraph; but does not include devices, or their components, parts or accessories."

4. The seized article does not purport to be nor is it represented to be a drug within the meaning of 21 U.S.C. 321(g). It is not intended for drug use (see Findings Numbers 9 and 10) and it is the intended use which determines its status under that Section. *United States* v. *3 Cartons, Etc.*, 132 F. Supp. 569, 573 (D. Calif. 1952); *United States* v. *46 Cartons, Etc.*, 113 F. Supp. 336 (D. N.J. 1953). Consequently, the article is not from a batch (of antibiotic drugs) with respect to which a certificate or release is required pursuant to 21 U.S.C. 357(a) and 357(c).

5. The fact that chemicals corresponding to those on the article under seizure are commonly used in other forms as drugs, is not persuasive on the issue before the Court, since neither the article as such nor the chemicals with which it is impregnated are intended for internal or external administration to patients.

6. The libelant has failed to support the allegations of the libel or information. Claimant is accordingly entitled to a dismissal of the libel with prejudice, and to a return of the seized article.

Final Decree

The above-styled cause having come on for trial commencing on or about May 18, 1965 before the Court sitting without a jury, witnesses' testimony for both sides having been taken and heard and argument of counsel having been given and heard in open court, and the Court being fully advised in the premises, it is

Ordered, Adjudged and Decreed, that:

The libel of information filed in the above-styled cause, be and the same is hereby dismissed with prejudice, and it is directed that the articles seized and attached in the said proceeding above referred to be returned to claimant, Difco Laboratories.

s/ Thomas P. Thornton

Dated: August 31, 1966.

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

[Title Omitted]

NOTICE OF APPEAL

[Filed October 21, 1966]

NOTICE IS HEREBY GIVEN that the United States of America, above-named libelant, hereby appeals to the United States Court of Appeals for the Sixth Circuit from the Final Decree entered in this matter on August 31, 1966 by the Honorable Thomas P. Thornton.

This NOTICE OF APPEAL being by the United States of America, no bond on appeal is being filed herewith.

Lawrence Gubow
United States Attorney

By s/ Milton J. Trumbauer, Jr.
Milton J. Trumbauer, Jr.
Assistant United States Attorney

Attorneys for
United States of America,
Libelant

817 Federal Building
Detroit, Michigan 48226

UNITED STATES COURT OF APPEALS
FOR THE SIXTH CIRCUIT

No. 17592

UNITED STATES OF AMERICA,
Plaintiff-Libellant, Appellant

v.

AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * *,
Defendant-Claimant, Appellee

ON APPEAL from the United States District Court for the Eastern District of Michigan, Southern Division.

Decided March 29, 1968

Before: COMBS, Circuit Judge, MCALLISTER and CECIL, Senior Circuit Judges.

CECIL, Senior Circuit Judge. This appeal involves a product known as Bacto-Unidisk which is described as a circular one-half inch wide cardboard having a diameter of just over three and one half inches, with eight circular paper units extending inwardly from the ring. Seven of these units are impregnated with different antibiotic drugs and the eighth one with sulfadiazine. The disc is referred to as a sensitivity unit.

The action arose out of condemnation of a quantity of product by the United States under the Food, Drug and Cosmetic Act, Section 301 et seq., Title 21, U.S.C. The government claims that the product (1) is a "drug" within the meaning of the Act, (2) is composed partly of specified antibiotic drugs, (3) was shipped in interstate commerce, and (4) was neither certified nor exempted from certification, as required by Section 357, Title 21,

U.S.C. This failure to obtain certification or exemption from certification, was alleged to render the product misbranded under Section 352(1), Title 21, U.S.C.

The threshhold question is whether Bacto-Unidisk, the product in question, is a drug within the meaning of Section 321(g), Title 21, U.S.C. That section provides

> "The term 'drug' means (1) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (2) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (3) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (4) articles intended for use as a component of any article specified in clauses (1), (2), or (3) of this paragraph; but does not include devices or their components, parts, or accessories."

The district judge held that it was not a drug as defined in the Act. We agree.

It is conceded that no part of the disc, which is the subject of the action, is administered to man or other animals, either internally or externally. It is used in hospital laboratories and in clinical practice to test the sensitivity or reaction of a specimen drawn from a patient to each of the antibacterial units contained on the disc—hence, the reference, sensitivity disc. The patient's specimen may be sputum, urine, throat swab or other matter withdrawn from his body. The sole function of the disc is to furnish medical doctors with information which enables them to treat diseases previously diagnosed.

If the statute has any application, it would have to be under subdivision (2), "articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals; * * *" The district judge said in his opinion, "When it comes right down to the determination which we must make, a literal reading of (g)(2) which defines 'drug' as 'articles intended for

use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals' clearly has application to the article libeled herein." This is only true in an indirect sense. Certainly it has nothing to do with diagnosis or prevention of disease. In itself it is not intended for use either internally or externally to cure, mitigate or treat disease. It only aids the physician to determine what antibiotics to use for the cure, mitigation or treatment of the patient's disease. We agree with the trial judge that it was not the legislative intent to apply the phrase "intended for use in the * * * cure, mitigation, treatment * * *" in such an indirect manner.

The district judge made Findings of Fact and Conclusions of Law. Finding of Fact 9 and Conclusion of Law 3 are as follows:

> "9. Sensitivity disks are not recognized in (admitted to) the United States Pharmacopeia or the National Formulary, which are 'official compendia' under the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321 (j)) nor are such disks the kind of articles which are accepted for admission to the official compendia because, among other reasons, they are not regarded by the Committees on Revision (admission) of the compendia as drugs within the commonly accepted meaning of that term in medical science. In medical science those substances which are for administration to or for use on, a person for the treatment of disease or injury, are regarded as drugs. This is the commonly accepted view of physicians generally. A physician who testified for libellant could think of no example of a substance not taken into or applied to the body which he would 'consider medically' as a drug."
>
> "3. In medical science the concept of 'drug' is limited to articles administered to man or other animals, either internally or externally. This is the generally accepted view among physicians (Finding Number 9). The evidence affords no basis for the conclusion that the definition of 'drug' in the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321(g)) was in-

tended by Congress to extend beyond the meaning of that term in medical science, to encompass these sensitivity disks. The definition of 'drug' is found in 21 U.S.C. 321(g).

We agree with the district judge and conclude that the Bacto-Unidisk, which is the subject of this action, is not a drug within the meaning of Section 321(g), Title 21, U.S.C. and is therefore not from a batch of antibiotic drugs to which a certificate or release is required pursuant to Section 357(a), (c), Title 21, U.S.C.

Authorities cited by counsel for appellant to the effect that such substances as honey, mineral water, cigarettes, peppermint leaves and human blood have been held to be drugs are not in point. Section 321(g), Title 21, U.S.C. defines "drug", in part, "as an article *'intended for use'* in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." (Emphasis added.) In holding honey,[1] mineral water,[2] cigarettes[3] and peppermint tea leaves[4] to be drugs, the courts based their opinions on the fact that by advertising these products as possessing therapeutic and medicinal powers, such products were "intended for use" as drugs and hence within the statutory definition. Whole human blood[5] which may be used in human blood transfusions clearly comes within the meaning of the statute.

Another question raised at the trial level and assigned as error on this appeal is that the claimant should be barred from raising the question that the seized article is not covered by the statute for the reason that it had not availed itself of permissible administrative procedure.

---

[1] *United States* v. *250 Jars . . . Honey*, 218 F. Supp. 208 (E.D. Mich. aff'd 344 F.2d 288 (C.A. 6).

[2] *Bradley* v. *United States*, 264 Fed. 79 (C.A. 5).

[3] *United States* v. *46 Cartons . . . Fairfax Cigarettes*, 113 F. Supp. 336 (D.N.J.).

[4] *United States* v. *Hohensee*, 243 F.2d 367 (C.A. 3), cert. den. 353 U.S. 976, rehearing den. 354 U.S. 927.

[5] *United States* v. *Calise*, 217 F. Supp. 705 (S.D.N.Y.).

The Food and Drug Administration has attempted in Part 147 of its regulations (21 C.F.R. 147 et seq.) to issue regulations applicable to sensitivity discs such as Bacto-Unidisks. The appellant claims that inasmuch as the claimant, after due notice, failed to seek judicial review of the above regulations, as provided by statute, he cannot collaterally attack their validity in an enforcement proceeding. See *Byrd* v. *United States*, 154 F.2d 62 (C.A. 5); *United States* v. *Bodine Produce Co.*, 206 F. Supp. 201 (D. Ariz.). However, unlike those cases which involved regulations pertaining to articles which were concededly within the jurisdiction of the Food and Drug Administration, the issue in this case is whether Bacto-Unidisk is a drug within the meaning of the statute and therefore not subject to any regulation of the Food and Drug Administration. Our function on this appeal is not to review the validity of the regulations to determine if they are supportable by substantial record evidence and not an abuse of administrative discretion, but to determine, based upon an interpretation of the statutory definition of a drug, whether the seized article is within the Administrator's jurisdiction. A claimant cannot be precluded from defending a libel action on the ground that the seized article is not covered by the statute.

The judgment of the District Court is affirmed.

Judgment of Court of Appeals

UNITED STATES COURT OF APPEALS
FOR THE SIXTH CIRCUIT

No. 17592

UNITED STATES OF AMERICA, *Libelant-Appellant*

vs.

AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * *

DIFCO LABORATORIES INCORPORATED, *Claimant-Appellee*

Before: COMBS, Circuit Judge, MCALLISTER and CECIL, Senior Circuit Judges.

JUDGMENT

[Filed March 29, 1968]

APPEAL from the United States District Court for the Eastern District of Michigan

THIS CAUSE came on to be heard on the record from the United States District Court for the Eastern District of Michigan and was argued by counsel.

ON CONSIDERATION WHEREOF, It is now here ordered and adjudged by this Court that the judgment of the said District Court in this cause be and the same is hereby affirmed.

No costs awarded. Rule 23(4).

Entered by order of the Court.

s/ Carl W. Reuss
Clerk

SUPREME COURT OF THE UNITED STATES

No. ———, October Term, 1968

UNITED STATES, PETITIONER

vs.

AN ARTICLE OF DRUG * * * BACTO-UNIDISK

ORDER EXTENDING TIME TO FILE PETITION FOR WRIT OF CERTIORARI

UPON CONSIDERATION of the application of counsel for petitioner,

IT IS ORDERED that the time for filing a petition for writ of certiorari in the above-entitled cause be, and the same is hereby, extended to and including July 26, 1968.

s/ Potter Stewart
Associate Justice of the Supreme Court of the United States

Dated this 18th day of June, 1968.

Letter Extending Time to Oppose Petition

[COPY]

OFFICE OF THE CLERK
SUPREME COURT OF THE UNITED STATES
WASHINGTON, D. C. 20543

August 13, 1968

Edward Brown Williams, Esq.
423 Washington Building
Washington, D. C. 20005

RE: UNITED STATES v. AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * *
No. 343, October Term, 1968

Dear Mr. Williams:

Your application for an extension of time to file a brief in opposition to the petition for a writ of certiorari in the above-entitled case has been granted, and the time has been extended to and including September 25, 1968.

Very truly yours,

John F. Davis,
Clerk

By
Michael Rodak, Jr.
Deputy Clerk

jmh

cc: The Honorable Erwin N. Griswold
Solicitor General of the United States
Department of Justice
Washington, D. C. 20530

SUPREME COURT OF THE UNITED STATES

No. 848, October Term, 1968

UNITED STATES, PETITIONER

v.

AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * *

ORDER ALLOWING CERTIORARI—Filed October 21, 1968

The petition herein for a writ of certiorari to the United States Court of Appeals for the Sixth Circuit is granted, and the case is placed on the summary calendar.

And it is further ordered that the duly certified copy of the transcript of the proceedings below which accompanied the petition shall be treated as though filed in response to such writ.

A true copy Test:

John F. Davis
Clerk of the Supreme Court
of the United States

By s/ E. P. Cullinan
Chief Deputy

[SEAL]

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In the Supreme Court of the United States

OCTOBER TERM, 1968

No.

UNITED STATES OF AMERICA, PETITIONER

v.

AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * *

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT

The Solicitor General, on behalf of the United States of America, petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Sixth Circuit in this case.

OPINIONS BELOW

The opinion of the court of appeals (App. A, *infra*) is reported at 392 F. 2d 21. The opinion of the district court (App. B, *infra*) is not reported.

JURISDICTION

The judgment of the court of appeals (App. C, *infra*) was entered on March 29, 1968. On June 18, 1968, Mr. Justice Stewart extended the time for filing a petition for a writ of certiorari to and including July 26, 1968. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

QUESTION PRESENTED

Whether the Secretary of Health, Education and Welfare correctly concluded that discs containing various antibotic drugs—discs which physicians use to select the antibiotic most appropriate to treat a particular patient—are "antibiotic drugs" under the Federal Food, Drug, and Cosmetic Act, and therefore are subject to the requirement in Section 507 of that Act that, pursuant to regulations of the Secretary, each such drug be tested by batches to insure its safety and efficacy.

STATUTE INVOLVED

The Federal Food, Drug, and Cosmetic Act, 52 Stat. 1040 (1938), as amended, 21 U.S.C. 301, *et seq.*, provides in part:

Sec. 201 [*21 U.S.C. (Supp. II) 321*]

For the purposes of this Act—

* * * * *

(g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure of any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C); but does not include devices or their components, parts or accessories.

* * * * *

(h) The term "device" * * * means instruments, apparatus, and contrivances, including their components, parts, and accessories, intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; or (2) to affect the structure of any function of the body of man or other animals.

Section 502 [*21 U.S.C. 352*]

A drug or device shall be deemed to be misbranded—

(*l*) If it is, or purports to be, or is represented as a drug composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other antibiotic drug, or any derivative thereof, unless (1) it is from a batch with respect to which a certificate or release has been issued pursuant to section 507, and (2) such certificate or release is in effect with respect to such drug: *Provided,* that this paragraph shall not apply to any drug or class of drugs exempted by regulations promulgated under section 507(e) or (d).

Section 507 [*21 U.S.C. 357*]

(a) The Secretary of Health, Education, and Welfare, pursuant to regulations promulgated by him, shall provide for the certification of batches of drugs composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other antibiotic drug, or any derivative thereof. A batch of any such drug shall be certified if such drug has such characteristics of identity and such batch has such characteristics of strength,

quality, and purity, as the Secretary prescribes in such regulations as necessary to adequately insure safety and efficacy of use, but shall not otherwise be certified. Prior to the effective date of such regulations the Secretary, in lieu of certification, shall issue a release for any batch which, in his judgment, may be released without risk as to the safety and efficacy of its use. Such release shall prescribe the date of its expiration and other conditions under which it shall cease to be effective as to such batch and as to portions thereof. For purposes of this section and of section 502(*l*), the term "antibiotic drug" means any drug intended for use by man [1] containing any quantity of any chemical substance which is produced by a microorganism and which has the capacity to inhibit or destroy microorganisms in dilute solution (including the chemically synthesized equivalent of any such substance).

(b) Regulations providing for such certifications shall contain such provisions as are necessary to carry out the purposes of this section, including provisions prescribing (1) standards of identity and of strength, quality, and purity; (2) tests and methods of assay to determine compliance with such standards; (3) effective periods for certificates, and other conditions under which they shall cease to be effective

[1] This definition was added by the Drug Amendments of 1962, P.L. 87-781, to extend the certification controls to all antibiotics intended for human use as contrasted with veterinary use. H. Rep. 2526, 87th Cong., 2d Sess., October 3, 1962, Conference Report, Statement of Managers on the Part of the House, pp. 21-22. See, also, Statement by Senator Kefauver, 108 Cong. Rec. 22089, October 3, 1962.

as to certified batches and as to portions thereof; (4) administration and procedure; and (5) such fees, specified in such regulations, as are necessary to provide, equip, and maintain an adequate certification service. Such regulations shall prescribe only such tests and methods of assay as will provide for certification or rejection within the shortest time consistent with the purposes of this section.

STATEMENT

Section 507 of the Federal Food, Drug, and Cosmetic Act, *supra,* confers upon the Secretary of Health, Education, and Welfare the duty to provide by regulation "for the certification of batches" of antibiotic drugs to make certain that they have such characteristics of strength, quality and purity as are necessary "to adequately insure safety and efficacy of use." This requirement of batch testing was first applied to penicillin in 1945 (59 Stat. 463). The need for the legislation arose out of the circumstances that (1) penicillin was produced by a biological process and was subject to the vagaries inherent in such processes; (2) the drug, if promptly effective and free from toxic impurities, was useful for treatment of a long list of life-threatening illnesses; and (3) the methods for assaying the drug were uncertain and variable in result. Because methods previously developed to assure quality control in the preparation of drugs were inadequate to deal with a substance having these characteristics, Congress concluded that only by testing each batch of the antibiotic prior to its dissemination could the public be assured of safety

and effectiveness. See H. Rep. 702, 79th Cong., 1st Sess. (1945), particularly the letter from the Acting Federal Security Administrator recommending the legislation, pp. 10–11. As new antibiotic drugs, with similar characteristics, were developed, the statute was extended to cover them, reaching its present generalized form in 1962.[2]

With the development of the many forms of antibiotics (including some which present a risk of undesirable or dangerous side effects, when administered to some patients), it became important in medical practice to have a screening test which would provide the physician with an accurate estimate as to which among several available antibiotics would be likely to be effective against the patient's infecting organism. See, *e.g.*, Petersdorf and Plorde, *The Usefulness of In Vitro Sensitivity Tests in Antibiotic Therapy,* Annual Review of Medicine, Vol. 14, pp. 41–56 (1963); Physician's Desk Reference, p. 908 (1968). Antibiotic sensitivity discs were developed commercially in 1949 or 1950 (R. 96a) to provide such a rapid screening test. In the beginning only three antibiotic drugs were involved. As new antibiotics were introduced into clinical practice, new discs were developed.

Respondent, the "Bacto-Unidisk," is a sensitivity unit containing seven antibiotic drugs and sulfadiazine. The outer portion of the disc is a circular ½-inch-wide piece of cardboard with a diameter of

[2] Batch certification was extended to streptomycin in 1947 (61 Stat. 11) and to aureomycin and others in 1949 (63 Stat. 409). About 30 antibiotics are now listed in the regulations appearing at 21 C.F.R. 145.3.

slightly over 3½ inches, resembling a bracelet. Extending inwardly from the ring are eight smaller circular units, each impregnated with one of the drugs. The name of each drug appears on the ring near the place where one of the impregnated circles is attached (R. 141a). In use, micro-organisms, in a specimen drawn from the patient (sputum, urine, throat swab, blood, pus, etc.) are cultured on an agar surface while in contact with the disc. Zones of inhibition of bacterial growth will appear 6 to 18 hours later around the antibiotic drugs to which the infecting organisms are sensitive, whereas no zones of inhibition will appear around the antibiotics that are not effective. This means that each of the antibiotic drugs has diffused from its area of the disc into the surrounding growth medium and has inhibited or not inhibited bacterial growth. From this reading, the physician is able to select one or another of the antibacterial agents for his patient's treatment (R. 11a, 13a, 31a–32a). It is undisputed on this record that the results of sensitivity testing guide the physician in his selection of a treating agent, and help him rule out agents which are not effective or which are less effective against the infection involved or which would needlessly present a risk of harmful side effects (R. 13a, 34a–35a, 38a, 43a, 47a–49a, 90a, 93a–94a, 100a, 103a).

In 1960, after notice (25 Fed. Reg. 3084) and an opportunity for public participation, the Commissioner of Food and Drugs, under authority delegated by the Secretary, promulgated regulations to require batch certification of dry powders of antibiotic drugs

used for sensitivity testing and of antibiotic sensitivity discs intended for use in diagnosis or treatment of disease (25 Fed. Reg. 9369). The order recited that sensitivity discs initially had been exempted from batch certification requirements, but that, following "numerous complaints by the medical profession, hospitals, and laboratory technicians, the Food and Drug Administration made an extensive survey" of the production and marketing of discs, and found them unreliable in their statements of potency with resultant impairment of their safety and effectiveness (25 Fed. Reg. 9370). It was therefore deemed "vital for the protection of the public health" (*ibid.*) to adopt regulations requiring batch certification of antibiotic sensitivity discs. The regulations are published at 21 C.F.R. 147.

This case arose as an *in rem* seizure proceeding against an interstate shipment of a number of cases of Bacto-Unidisk, which the complaint alleged (1) were "drugs" within the meaning of the Act, (2) were composed of specific antibiotic drugs, and (3) were neither certified nor exempted from certification, as required by Section 507 of the Act, and the regulations issued thereunder (R. 4a–5a). Difco Laboratories, which produces the discs, admitted the allegations, except that it denied that the articles were "drugs," and thus that they were subject to batch certification requirements under the statute.

The district court held that, although the discs come within the definition of "drug" in Section 201(g) of the Act, read literally, and despite the fact that "drugs" were contained therein, the discs were not

"drugs" since no part thereof is administered to man or other animals, either internally or externally, and the disc "does not purport to be and is not represented as a 'drug' as that term is used in medical science or by physicians generally" (App. B, *infra*, pp. 10a–11a, 15a). The court suggested, without deciding, that the discs would more appropriately be classified as "devices" under Section 201(h) of the act, *supra* (App. B, *infra*, pp. 10a–11a).

The Court of Appeals for the Sixth Circuit affirmed, stating that the sole function of the disc is to furnish doctors with information which enables them to treat diseases previously diagnosed; that the discs have nothing to do with diagnosis or prevention of disease; and that, although the discs aid physicians in the determination of what antibiotic to use for the cure, mitigation or treatment of disease, Congress did not intend to apply the statutory phrase "intended for use in the * * * cure, mitigation, [or] treatment" in such an indirect manner (App. A, *infra*, p. 3a).

REASONS FOR GRANTING THE WRIT

This case presents an issue of vital importance to the public health and of general importance in the administration of the Federal Food, Drug, and Cosmetic Act. The courts below have overturned the informed judgment of the Secretary, based on extensive study and a formal rule-making proceeding, that the Act's requirements of batch testing must be applied to the respondent discs in order to protect the public. The courts rejected this conclusion on the basis of their belief as to the common medical usage of the

statutory term "drug," without regard to the statutory definition of the term or to principles of statutory interpretation which this and other courts have developed. In so doing, the courts below have erroneously deprived the public of the only statutory protection which is adequate to assure that antibiotic sensitivity discs will be safe and efficacious in use.

1. Proper selection of a safe and effective drug in treating infections, particularly when the infection is refractory and life-threatening, depends in substantial measure upon the reliability of antibiotic discs, such as the Bacto-Unidisk, to aid the physician in promptly identifying the drug that is best for administration to his critically-ill patient. Indeed, the labeling for most of the antibiotics available to prescribers tells the physician that his use of these drugs should depend upon the results of *in vitro* culture and sensitivity testing.[3]

The physician on the front line of clinical practice must accept the discs as having their professed identity, strength, and quality, and as suitable to yield the results claimed in the labeling. The physician does not have the time, the skills, the facilities or the experimental patients needed to test the discs for potency and performance before using them to test the sensitivity of his patient's infection to the array of antibiotic drugs packaged on the disc (R. 101a). Con-

[3] See, *e.g.*, Lincocin (lincomycin), Physicians' Desk Reference (1968), p. 1173: "As with all antibiotics, *in vitro* culture and susceptibility testing should be performed before Lincocin is utilized as sole antibiotic therapy." See, also, Abbocillin, *id.* at 502; Polycillin, *id.* at 580; Prostaphlin, *id.* at 585.

gress recognized that it is vitally important to batch-test, for example, tablets of penicillin to assure that they have the declared potency and that they will dissolve properly and be transmitted into the patient's blood stream to treat his infection. Under the general standards enacted by Congress, the Commissioner of Food and Drugs has determined in a rule-making proceeding that it is equally important to test the antibiotics on discs to determine that each contains the specified potency of the declared antibiotic drug, and that each will properly diffuse from the tip into the bacterial growth medium to disclose whether it has an inhibitory effect on the bacterial microorganisms responsible for the patient's infection. The lives of critically ill patients may well be jeopardized if the discs contain excessive or deficient potencies of any of the drugs or if any of the drugs diffuse too rapidly or too slowly. Any such inaccuracy can result in a false reading of the sensitivity of the patient's infection to particular antibiotics.

The basic question here is whether the special procedures which Congress found necessary to assure the safe and effective use of antibiotics may properly be applied to discs which are impregnated with antibiotics and which are the means of determining which of such drugs to administer to a patient. It is the government's position that batch testing of such discs manifestly falls within the purpose for which the special procedures of Section 507 were developed, and that there is no reason to interpret the Act in such a way as to preclude the premarketing certification of

the discs. The purpose of section 507 is to make certain that antibiotics will be safe and effective in use. Without batch testing of the discs, there can be no assurance that the antibiotics administered to patients will satisfy that standard.[4]

2. The fundamental error of the courts below lies in their application of what they believed to be the common medical usage of the term "drug" to a complex, technical, regulatory scheme designed for protection of the public health, without regard to either the statutory definition of the term or the purpose of the statute. The courts below thereby disregarded the important principles of statutory interpretation set forth by this Court in *Securities and Exchange Commission* v. *Ralston Purina Co.*, 346 U.S. 119, 124–125. There, in interpreting a statutory exemption from registration of a private offering of stock, the Court said that the "natural way to interpret the private offering exemption is in light of the statutory purpose." Finding that it was the Congressional intent to exempt transactions as to which there

[4] At issue here is the right to exercise pre-clearance market controls, not only as to discs manufactured by Difco, but as to the other companies (presently three in number) engaged in the production and interstate distribution of the same sort of sensitivity units. One of these companies is under a permanent injunction restraining it from introducing into interstate commerce any antibiotic sensitivity units that have not been tested and certified (R. 157–162a).

Moreover, the reasoning of the courts below would equally preclude the requirement of batch certification of the antibiotics prior to their being impregnated onto the sensitivity discs, so long as antibiotics manufactured for that purpose are not commingled with those intended to be administered to patients.

was no practical need for the statute's application, the Court ruled that the interpretation of the exemption "should turn on whether the particular class of persons affected needs the protection of the Act." Applying this standard, the Court held, without any reference to usage of the term "public offering" outside the statute, that Ralston Purina's offering of treasury stock to its "key employees" was a "public offering" subject to the protections of the Securities Act because the employees had not been "shown to be able to fend for themselves * * *" (*id.* at 125).[5]

Here, as the district court admitted (App. B, *infra*, p. 10a), the discs do fall within the literal definition of "drugs" in Section 201(g), which is not limited to articles recognized in the official United States Pharmacopoeia, but alternatively includes "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease."[6] Despite a contrary suggestion by the court of appeals, the discs are clearly used in the cure, mitigation, and treatment of disease. The real question in the case is how to draw

[5] Indeed, there is even more reason in the present case than in *Ralston Purina* to be guided by the policy of the statute, and to eschew reference to usage outside the statute, in construing the statutory term at issue. The term "public offering" was nowhere defined in the Securities Act (see 346 U.S. at 122). By contrast, the word "drug" is defined in Section 201(g) of the Food and Drug Act for "the purposes of this Act"—it is therefore a statutory term of art whose usage outside the Act is legally irrelevant to its statutory meaning.

[6] Application of the discs to a specimen drawn from a human being is also unquestionably "use by man" within the meaning of Section 507(a), as contrasted with veterinary use. See *supra*, p. 4, n. 1.

the line between "drug"[7] as defined in Section 201(g) and "device" which is defined in section 201(h) as "instruments, apparatus, and contrivances * * * intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease * * *." Since the literal words overlap, the "natural way" to draw the line, as *Ralston-Purina* explained, "is in light of the statutory purpose." The qualities of antibiotics which led Congress to impose the requirement of batch testing are the same whether the drug is used for a pill, for a hypodermic injection, or as a test to determine what pill or injection to administer. The need for assurance as to quality and potency is as great when the antibiotic is used on a disc as when it is used in a pill or injection. Not only are physicians equally unable to make tests to determine potency, etc., whether the antibiotic is used in a pill or injection or on the disc; but patients—the class of persons that the Act is designed to protect—will derive little benefit from the Act's purpose of assuring that the antibiotic drugs administered to them are safe and properly potent if unreliability of the antibiotic sensitivity discs results in administration of the wrong drug to them.

In short, the whole purpose of batch testing of antibiotics for safety and efficacy of use applies to the discs of antibiotics. It was, therefore, entirely reasonable for the Secretary to consider the discs as drugs under Section 201(g), subject to the batch testing

[7] Section 507(a), *supra* pp. 3–4, which imposes the batch certification requirement, defines "antibiotic drug" as "any drug * * *"

requirements of Section 507. There was no adequate reason for the rejection by the courts below of the statutory interpretation arrived at in a rule-making proceeding conducted by the officials entrusted with the responsibility of administering this important public health legislation. Indeed, there was every reason to uphold that interpretation as consistent with the statutory language and in furtherance of the statutory purpose.

3. The Federal Food, Drug, and Cosmetic Act is properly given a broad construction in accord with its purpose to protect the public health. *United States* v. *Sullivan*, 332 U.S. 689. In *AMP, Inc.* v. *Gardner*, 389 F. 2d 825, 830 (C.A. 2), pending on petition for certiorari, No. 86, this Term, the Second Circuit rejected the idea that this important public law was "restricted to products commonly called 'drugs'." And long before that, the Court of Appeals for the Fifth Circuit, interpreting the "drug" definition of the 1906 Food and Drugs Act, rejected as "entirely too narrow" a contention that spring water could not be treated as a "drug" under the Act because of definitions of "drug" found in dictionaries and pharmacopoeias. *Bradley* v. *United States*, 264 Fed. 79. While, as we pointed out in our brief in opposition in the *AMP* case, those decisions are not directly in conflict with the decision below since the articles there involved were administered into the human body, the decisions do represent a conflicting approach to the interpretation of the Act, rejecting common usage as determinative of what constitutes a drug. Those decisions take what we believe to be the correct approach, *i.e.*, they apply the Act functionally

to afford the public the protections of the statute that are scientifically pertinent to the characteristics of the particular article at issue and to the medical use for which it is intended. The contrary judicial approach to the interpretation of the Act taken in this case is of great significance, not only in its application to the particular article at issue here, but in the general administration of the statute.

CONCLUSION

For the reasons stated, it is respectfully submitted that the petition for a writ of certiorari should be granted.

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JULY 1968.

APPENDIX A

No. 17592

(Filed March 29, 1968)

United States Court of Appeals for the Sixth Circuit

UNITED STATES OF AMERICA, PLAINTIFF-LIBELLANT, *v.* AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * * DEFENDANT-CLAIMANT, APPELLEE

On Appeal from the United States District Court for the Eastern District of Michigan, Southern Division

Decided March 29, 1968.

Before COMBS, Circuit Judge, MCALLISTER and CECIL, Senior Circuit Judges

CECIL, Senior Circuit Judge. This appeal involves a product known as Bacto-Unidisk which is described as a circular one-half inch wide cardboard having a diameter of just over three and one half inches, with eight circular paper units extending inwardly from the ring. Seven of these units are impregnated with different antibiotic drugs and the eighth one with sulfadiazine. The disc is referred to as a sensitivity unit.

The action arose out of condemnation of a quantity of the product by the United States under the Food, Drug and Cosmetic Act, Section 301 et seq., Title 21, U.S.C. The government claims that the product (1) is a "drug" within the meaning of the Act, (2) is composed partly of specified antibiotic drugs, (3) was shipped in interstate commerce, and (4) was neither certified nor exempted from certification, as required

by Section 357, Title 21, U.S.C. This failure to obtain certification or exemption from certification, was alleged to render the product misbranded under Section 352(1), Title 21, U.S.C.

The threshold question is whether Bacto-Unidisk, the product in question, is a drug within the meaning of Section 321(g), Title 21, U.S.C. That section provides

> "The term 'drug' means (1) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (2) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (3) articles (other than food) intended to affect the structure or any function of the body of a man or other animals; and (4) articles intended for use as a component of any article specified in clauses (1), (2), or (3) of this paragraph; but does not include devices or their components, parts, or accessories."

The district judge held that it was not a drug as defined in the Act. We agree.

It is conceded that no part of the disc, which is the subject of the action, is administered to man or other animals, either internally or externally. It is used in hospital laboratories and in clinical practice to test the sensitivity or reaction of a specimen drawn from a patient to each of the antibacterial units contained on the disc—hence, the reference, sensitivity disc. The patient's specimen may be sputum, urine, throat swab or other matter withdrawn from his body. The sole function of the disc is to furnish medical doctors with information which enables them to treat diseases previously diagnosed.

If the statute has any application, it would have to be under subdivision (2), "articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals; * * *" The district judge said in his opinion, "When it comes right down to the determination which we must make, a literal reading of (g)(2) which defines 'drug' as 'articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals' clearly has application to the article libeled herein." This is only true in an indirect sense. Certainly it has nothing to do with diagnosis or prevention of disease. In itself it is not intended for use either internally or externally to cure, mitigate or treat disease. It only aids the physician to determine what antibiotics to use for the cure, mitigation or treatment of the patient's disease. We agree with the trial judge that it was not the legislative intent to apply the phrase "intended for use in the * * * cure, mitigation, treatment * * *" in such an indirect manner.

The district judge made Findings of Fact and Conclusions of Law. Finding of Fact 9 and Conclusion of Law 3 are as follows:

> "9. Sensitivity disks are not recognized in (admitted to) the United States Pharmacopoeia or the National Formulary, which are 'official compendia' under the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321(j)) nor are such disks the kind of articles which are accepted for admission to the official compendia because, among other reasons, they are not regarded by the Committees on revision (admission) of the compendia as drugs within the commonly accepted meaning of that term in medical science. In medical science those substances which are for administration to or for

use on, a person for the treatment of disease or injury, are regarded as drugs. This is the commonly accepted view of physicians generally. A physician who testified for libellant could think of no example of a substance not taken into or applied to the body which he would 'consider medically' as a drug."

"3. In medical science the concept of 'drug' is limited to articles administered to man or other animals, either internally or externally. This is the generally accepted view among physicians (Finding Number 9). The evidence affords no basis for the conclusion that the definition of 'drug' in the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321(g)) was intended by Congress to extend beyond the meaning of that term in medical science, to encompass these sensitivity disks. The definition of 'drug' is found in 21 U.S.C. 321(g).

We agree with the district judge and conclude that the Bacto-Unidisk, which is the subject of this action, is not a drug within the meaning of Section 321(g), Title 21, U.S.C. and is therefore not from a batch of antibiotic drugs to which a certificate or release is required pursuant to Section 357(a), (c), Title 21, U.S.C.

Authorities cited by counsel for appellant to the effect that such substances as honey, mineral water, cigarettes, peppermint leaves and human blood have been held to be drugs are not in point. Section 321(g), Title 21, U.S.C. defines "drug", in part, "as an article *'intended for use'* in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." (Emphasis added.) In holding honey,[1] min-

[1] *United States* v. *250 Jars . . . Honey*, 218 F. Supp. 208 (E.D. Mich., aff'd 344 F.2d 288 (C.A. 6).

eral water,[2] cigarettes[3] and peppermint tea leaves[4] to be drugs, the courts based their opinions on the fact that by advertising these products as possessing therapeutic and medicinal powers, such products were "intended for use" as drugs and hence within the statutory definition. Whole human blood[5] which may be used in human blood transfusions clearly comes within the meaning of the statute.

Another question raised at the trial level and assigned as error on this appeal is that the claimant should be barred from raising the question that the seized article is not covered by the statute for the reason that it had not availed itself of permissible administrative procedure.

The Food and Drug Administration has attempted in Part 147 of its regulations (21 C.F.R. 147 et seq.) to issue regulations applicable to sensitivity discs such as Bacto-Unidisks. The appellant claims that inasmuch as the claimant, after due notice, failed to seek judicial review of the above regulations, as provided by statute, he cannot collaterally attack their validity in an enforcement proceeding. See *Byrd* v. *United States*, 154 F.2d 62 (C.A. 5); *United States* v. *Bodine Produce Co.*, 206 F. Supp. 201 (D. Ariz.). However, unlike those cases which involved regulations pertaining to articles which were concededly within the jurisdiction of the Food and Drug Administration, the issue in this case is whether Bacto-Unidisk is a drug within the meaning of the statute and therefore

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[2] *Bradley* v. *United States*, 264 Fed. 79 (C.A. 5).

[3] *United States* v. *46 Cartons . . . Fairfax Cigarettes*, 113 F. Supp. 336 (D.N.J.).

[4] *United States* v. *Hohensee*, 243 F.2d 367 (C.A. 3), cert. den. 355 U.S. 976, rehearing den. 354 U.S. 927.

[5] *United States* v. *Calise*, 217 F. Supp. 705 (S.D.N.Y.).

not subject to any regulation of the Food and Drug Administration. Our function on this appeal is not to review the validity of the regulations to determine if they are supportable by substantial record evidence and not an abuse of administrative discretion, but to determine, based upon an interpretation of the statutory definition of a drug, whether the seized article is within the Administrator's jurisdiction. A claimant cannot be precluded from defending a libel action on the ground that the seized article is not covered by the statute.

The judgment of the District Court is affirmed.

APPENDIX B

Memorandum Opinion

(Filed July 21, 1966)

When is a drug not a drug? When it is a part of a device or contrivance *not* for administration to man or animals, says the claimant. A drug is never "not a drug" says libelant—once a drug, always a drug. And this approximates the semantical conflict brought to a pinnacle by the conclusion of a trial before this Court, sitting without a jury.

A number of medical doctors testified as to the function performed by the libeled article and as to their understanding of the word "drug". Their testimony was not such as to compel a specific conclusion on the merits of this controversy, despite the fact that it was both interesting and enlightening.

The United States of America, libelant herein, filed a Libel of Information against the article, as per caption in the above title, seeking a decree of condemnation as to it pursuant to the provisions of the Federal Food, Drug and Cosmetic Act (21 U.S.C.A. § 334). Paragraph 4 sets forth the basis for the libel. It reads as follows:

"4. That the aforesaid article was misbranded when introduced into and while in interstate commerce within the meaning of the Federal Food, Drug and Cosmetic Act, 21 U.S.C.[A.]as follows:

352(1) in that article *purports to be and is represented as a drug* composed in part of penicillin, streptomycin, chloromycin, tetracycline, and aureomycin, and it is not from a batch with respect to which a certificate or release is in effect pursuant to 21 U.S.C. 357(a) and 357(c) and the article is not exempt from such requirements." (Emphasis supplied.)

Let us at the outset describe the article involved here. It is referred to as a sensitivity disk—the package bears the legend "Bacto-Unidisk for Antibiotic Sulfonamides A–S #1 Low Conc. Code 7011." The disk itself is a circular piece of ½ inch wide cardboard, having a diameter of just under 3½ inches. It resembles a bracelet. At evenly spaced intervals are printed the following words: "Penicillin", "Chlor", "S'Diazine", "Terra", "Erythro", "Tetra", 'Streptomycin", and "Aureo". Extending inwardly from the ring directly in front of each word is a small circular paper unit approximately ½ inch in diameter. Each such paper unit is impregnated with the chemical whose name appears closest to it on the ring. A Xerox reproduction of the article appears as an appendix hereto. Each such chemical is commonly used as an antibiotic drug, excepting sulphadiazine. The disk is referred to as a sensitivity unit. We will refer to each of the eight units as a sensitivity unit. The function of each sensitivity unit is to serve as an indication of the sensitivity or reaction of specimen from a patient to the particular chemical contained in the sensitivity unit. The patient's specimen may be in

the form of sputum, urine, throat swab, or other matter which has been withdrawn from the body of the patient. The reaction of the specimen serves as a guide to a medical doctor in his determination of the choice of antibiotic to prescribe for the patient. Perhaps the specimen reaction will indicate that the chemical contained in one sensitivity unit is more effective than that in another. The testimony in this case was to the effect that frequently a doctor has a choice of several antibiotic drugs to prescribe, with no persuasive basis for selecting one or another. The information obtained from the sensitivity disk may serve as a guideline to a doctor in choosing among several drugs, for administration to a patient, which without such information would be equal choice-wise. The testimony was that the disk is not primarily used in determining *whether* or not to prescribe an antibiotic, or sulphadiazine, but rather to aid in the choice of *which* antibiotic, including sulphadiazine, may be preferable. It appears to the Court that the use of the sensitivity disk in obtaining information provides a short cut. We are all familiar with situations where a particular antibiotic has been prescribed for a patient, taken by or administered to such patient with unsatisfactory results, requiring the prescribing of a different antibiotic which proves to be effective. It would seem that the use of the information obtained from the disk sensitivity test provides a means for eliminating much of the trial and error approach on the patient by screening out the non-advisable antibiotics without experimentation on the patient himself. In other words, the disk sensitivity units may serve as sort of guinea pigs, instead of the patients.

Claimant here challenges the conclusion of the Commissioner of Food and Drugs that its sensitivity disks are certifiable antibiotic drugs. Claimant takes no is-

sue with the language contained in 21 U.S.C.A. § 352 (1), quoted above. It does, however, take issue with the libelant's construction of 21 U.S.C.A. § 321(g)(2). We quote below the language of said subsection which is contained in the Definitions section of the Federal Food, Drug and Cosmetic Act:

21 U.S.C.A., § 321(g)

"(g) The term 'drug' means (1) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (2) *articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals;* and (3) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (4) articles intended for use as a component of any article specified in clause (1), (2), or (3) of this paragraph; but does not include devices or their components, parts or accessories." (Emphasis supplied.)

It is the position of libelant that subsection (2) of the above has direct application to the libeled article herein. It is the position of claimant that such a strained construction of subsection (2) is completely unwarranted and contrary to the intendment of the definition. This brings us back to our initial query as to when a drug is not to be considered a drug. When asked whether he considered that "sensitivity disks are drugs in the medical sense or the scientific sense," one medical doctor witness answered: "I would have to say that it is drug usage in a scientific sense." (Transcript, page 99) The same witness testified as follows in answering the following question: (Transcript, page 100)

"Q. Are you saying any more than that the information derived from these sensitivity tests is used as a sort of guideline in treatment, for example?

A. No. I think that it would be a very fair statement. As a guideline. It helps the antibiotic choice to be given."

Again this witness, Dr. Charles K. Wolfe, Jr., gave the following answer to the question propounded: (Transcript, page 103)

"Q. Let's see. Do you have an example of something which is not taken into the body or is not applied to the body which you consider medically as a drug?

A. I don't believe I can think of one offhand."

Counsel on each side of this controversy have presented able arguments, both orally and in brief form, as to their respective positions and contentions. When it comes right down to the determination which we must make, a literal reading of (g) which defines "drug" as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" clearly has application to the article libeled herein. Our reluctance to make this finding and conclusion our holding is due to the fact that it appears to us to be ridiculous and contrary to common sense. We are all the more convinced of this in the light of the definition appearing in the paragraph immediately following (g), which reads as follows:

"(h) The term 'device' (except when used in paragraph (n) of this section and in sections 331(i), 343(f), 352(c), and 362(c) of this title) means instruments, apparatus, and contrivances, including their components, parts, and accesso-

ries, intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; or (2) to affect the structure or any function of the body of man or other animals."

We are not here called upon to decide if the disk is a device, but it appears to us that consideration of it in this category under (h) is far more appropriate than consideration of it as a drug within the purview of (g). In view of our conclusion that the libeled article does not come within the purview of the definition of "drug" (21 U.S.C.A. § 321(g)), we deem it unnecessary to discuss other arguments advanced during the trial of this cause relating to side aspects of the issue. We are persuaded that the legislative intent here should not be interpreted to include this sensitivity disk as a drug, despite the fact that drugs are contained in the article, for the reason that no part of this article is administered to man or other animals, either internally or externally, and that its sole function is to provide medical doctors with information for use by them as guidelines.

Appropriate findings and conclusions may be submitted.

Thomas P. Thornton
United States District Judge

July 21, 1966.

FINDINGS OF FACT AND CONCLUSIONS OF LAW—

(Filed August 31, 1966)

FINDINGS OF FACT

1. A libel of information was filed in this Court on May 25, 1962, by the United States (hereinafter "libelant") praying seizure and condemnation, pursuant to the Federal Food, Drug and Cosmetic Act (21

U.S.C. 334) of an article alleged to be an antibiotic drug. By order of the Court entered May 25, 1962, the said article was attached by the United States Marshal.

2. The seized article was shipped from Buffalo, New York by Sterilon Corporation to claimant, Difco Laboratories, in the State of Michigan, on or about March 20, 1962.

3. The article consisted of 5 cases of 55 cartons each, each carton containing 50 clear plastic envelopes labled in part "Bacto-Unidisk for antibiotics Sulfonamides A-S #1 Low Conc. Tetra Streptomycin Aureo Penicillin Chlor S'Diazine Terra Erythro Code 7011", with a package insert entitled "Sensitivity Testing".

4. It was alleged in the libel that the article was misbranded when introduced into and while in interstate commerce within the meaning of 21 U.S.C. 352 (1) in that it purports to be and is represented as a drug composed in part of penicillin streptomycin, Chloromycetin, (chloramphenicol), tetracycline, and Aureomycin (chlortetracycline), that it is not from a batch with respect to which a certificate or release is in effect pursuant to 21 U.S.C. 357(a) and 357(c), and that the article is not exempt from such requirements.

5. Claimant, a corporation organized under the laws of the State of Michigan, filed a claim of ownership to the seized article and prayed to defend accordingly. Thereafter Claimant filed its answer and an amended answer.

6. Bacto-Unidisks, the brand name of the article seized, referred to generically as "sensitivity disks", are reagents used in laboratory testing of the sensitivity or resistance of microorganisms to chemicals corresponding to those with which the disks have been impregnated. The sensitivity disks in question are

composed of eight paper units extending inward from a paper ring, each of seven of which is impregnated with a different chemical corresponding to a chemical commonly used as an antibiotic drug, and an eighth with a chemical (sulfadiazine) which corresponds to a chemical commonly used as a drug but which is not an antibiotic (Tr. 28–29, 87, 185–186, 239–240).

7. Preliminary to the sensitivity testing procedure a plated agar culture medium is inoculated with a specimen taken from the body of a patient (such as sputum, blood, urine), incubated for an 18-hour period, and then, after proper preparation, the suspect organism is placed on a slide and observed microscopically for identification. In the subsequent sensitivity testing procedure the organism so identified is isolated and transferred to an appropriate agar culture medium on a Petri plate, the sensitivity disk is placed upon the culture medium, and the plate containing the agar and the disk are incubated, usually for an additional 18 hours to permit the organism to grow. A "zone of inhibition" (an area in which the organism does not grow) around the disk indicates that the organism is sensitive to the chemical on the disk. The absence of a zone of inhibition indicates that the organism is resistant to the chemical (see Transcript references in Finding Number 6 and Tr. 33–35, 188).

8. The information obtained from the sensitivity testing procedure outlined in Finding Number 7 is used by the physician as a guideline to treatment of the patient (Tr. 29–30, 37, 40, 48–50, 94, 100, 107, 167, 191). The disk, the culture medium, the Petri plate, and the incubation are all a part of the testing procedure yielding this information. Such information could not be obtained from the disk itself. The test is only one of many sources (such as the physician's

experience, clinical symptoms, the literature, and other tests such as urinalysis and blood serum tests) of the information upon which the physician relies in determining the treatment to be administered (Tr. 45–46, 53–54, 67–68, 108–110, 116–119, 145, 186–187, 240–241). The physician, frequently in emergency situations, selects and administers an antibiotic from the several (or "battery") usually available for the specific condition of the patient, without awaiting the results of the sensitivity test (Tr. 66–67, 88–89, 103–105). In such cases those results are then used by him to confirm his selection.

9. Senitivity disks are not recognized in (admitted to) the United States Pharmacopoeia or the National Formulary, which are "official compendia" under the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321 (j), Tr. 273, 307), nor are such disks the kind of articles which are accepted for admission to the official compendia because, among other reasons, they are not regarded by the Committees on Revision (admission) of the compendia as drugs within the commonly accepted meaning of that term in medical science (Tr. 274–276, 301–302, 307–308, 317). In medical science those substances which are for administration to or for use on, a person for the treatment of disease or injury, are regarded as drugs (Tr. 102–103, 195, 199, 261–262, 283). This is the commonly accepted view of physicians generally. A physician who testified for libelant could think of no example of a substance not taken into or applied to the body which he would "consider medically" as a drug (Tr. 103).

10. The substances on the libeled disks are commonly used in other forms (tablets, ampules, etc.) in medical practice as drugs and are recognized as such in the official compendia (Tr. 308–309.). The libeled article, although consisting in part of chemicals which

are used as drugs when prepared in appropriate dosage forms for such use, is not intended to be used as a drug in the medical sense, since no part of it is to be administered to patients, either internally or externally. Similarly, the several substances with which the article is impregnated are not intended to be introduced into or applied to the human body when used on the disk.

11. The article does not purport to be and is not represented as a "drug" as that term is used in medical science or by physicians generally. It is labeled "For Laboratory Use" (Exhibit No. 1; Tr. 196–198).

CONCLUSIONS OF LAW

1. This Court has jurisdiction by virtue of 21 U.S.C. Section 334.

2. Only antibiotic drugs are subject to certification under 21 U.S.C. Section 357(a) and 357(c).

3. In medical science the concept of "drug" is limited to articles administered to man or other animals, either internally or externally. This is the generally accepted view among physicians (Finding Number 9). The evidence affords no basis for the conclusion that the definition of "drug" in the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321(g)) was intended by Congress to extend beyond the meaning of that term in medical science, to encompass these sensitivity disks. The definition of "drug" is found in 21 U.S.C. 321(g), which reads as follows:

> "The term 'drug' means (1) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (2) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other

animals; and (3) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (4) articles intended for use as a component of any article specified in clause (1), (2), or (3) of this paragraph; but does not include devices, or their components, parts or accessories."

4. The seized article does not purport to be nor is it represented to be a drug within the meaning of 21 U.S.C. 321(g). It is not intended for drug use (see Findings Numbers 9 and 10) and it is the intended use which determines its status under that Section. *United States* v. *3 Cartons, Etc.*, 132 F. Supp. 569, 573 (D. Calif. 1952); *United States* v. *46 Cartons, Etc.*, 113 F. Supp. 336 (D. N.J. 1953). Consequently, the article is not from a batch (of antibiotic drugs) with respect to which a certificate or release is required pursuant to 21 U.S.C. 357(a) and 357(c).

5. The fact that chemicals corresponding to those on the article under seizure are commonly used in other forms as drugs, is not persuasive on the issue before the Court, since neither the article as such nor the chemicals with which it is impregnated are intended for internal or external administration to patients.

6. The libelant has failed to support the allegations of the libel or information. Claimant is accordingly entitled to a dismissal of the libel with prejudice, and to a return of the seized article.

FINAL DECREE

The above-styled cause having come on for trial commencing on or about May 18, 1965 before the Court sitting without a jury, witnesses' testimony for both sides having been taken and heard and argument

of counsel having been given and heard in open court, and the Court being fully advised in the premises, it is

Ordered, Adjudged and Decreed, that:

The libel of information filed in the above-styled cause, be and the same is hereby dismissed with prejudice, and it is directed that the articles seized and attached in the said proceeding above referred to be returned to claimant, Difco Laboratories.

Thomas P. Thornton
United States District Judge

Dated: August 31, 1966.

APPENDIX C

United State Court of Appeals for the Sixth Circuit

No. 17,592

(Filed March 29, 1968)

Carl W. Reuss, Clerk

UNITED STATES OF AMERICA, LIBELANT-APPLICANT, *vs.* AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * * DIFCO LABORATORIES INCORPORATED, CLAIMANT-APPELLEE

Before COMBS, Circuit Judge, MCALLISTER and CECIL, Senior Circuit Judge

JUDGMENT

APPEAL from the United States District Court for the Eastern District of Michigan

THIS CAUSE came on to be heard on the record from the United States District Court for the Eastern District of Michigan and was argued by counsel.

ON CONSIDERATION WHEREOF, It is now here ordered and adjudged by this Court that the judgment of the District Court in this cause be and the same is hereby affirmed.

No costs awarded. Rule 23(4).

Entered by order of the Court.

CARL W. REUSS,
Clerk.

U.S. GOVERNMENT PRINTING OFFICE: 1969

SUPREME COURT, U. S.

SEP 25 1968

JOHN F. DAVIS, CLERK

No. 343

IN THE

Supreme Court of the United States

OCTOBER TERM, 1968

UNITED STATES OF AMERICA,
Petitioner,

v.

AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * *

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Sixth Circuit

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BRIEF FOR CLAIMANT DIFCO LABORATORIES, INC. IN OPPOSITION

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OPINIONS BELOW

The opinion of the court of appeals (Pet. App. A) is reported at 392 F.2d 21. The opinion and findings of fact and conclusions of law of the district court (Pet. App. B) are not reported.

JURISDICTION

The judgment of the court of appeals (Pet. App. C) was entered on March 29, 1968. On June 18, 1968, Mr. Justice Stewart extended the time for filing a petition for a writ of certiorari to and including July 26, 1968. On August 13, 1968, time for filing a brief in opposition to the petition was extended to and including September 25,

1968. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

QUESTION PRESENTED

Whether a sensitivity disk utilized as part of a laboratory testing procedure which yields information the physician may use as a guideline to the changing or selection of an antibiotic to treat patients who have not responded to initial therapy, is a "drug" within the meaning of Section 201(g)(1)(B) of the Federal Food, Drug, and Cosmetic Act and, if it is a "drug", whether it is subject to batch certification under Section 507 of the Act.

STATUTE INVOLVED

The Federal Food, Drug, and Cosmetic Act, 52 Stat. 1040 (1938), as amended, 21 U.S.C. 301, et seq., provides in part:

Sec. 502 (21 U.S.C. 352)

A drug or device shall be deemed to be misbranded—

(a) if its labeling is false or misleading in any particular.

Sec. 505 (21 U.S.C. 355)

(a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the

methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug. * * *

STATEMENT

Petitioner's statement of the case does not accurately reflect the facts material to the question here presented.

The history of antibiotic certification (Pet. 5-6), indicates that there was a need for certification of antibiotic drugs because of variability of product and the side effects associated with some such drugs. The drugs involved were, however, those administered to or applied to patients and it was on the basis of this use that Congress provided for certification. The Bacto-Unidisk is not administered to or applied to patients. The history recited in the petition is therefore irrelevant to the question of certification of the disks and lends no support to petitioner's attempt to find a public health issue in this case, *viz.*, the alleged need for certification of sensitivity disks to avoid danger to the health of patients. As will be shown hereinafter, the two witnesses of Petitioner questioned on the matter were unable to support this position at the trial and a third witness affirmatively rejected it as invalid.

The case then becomes merely one of statutory interpretation.

The question decided in the courts below was whether sensitivity disks are used in the diagnosis or treatment of disease and are, therefore, drugs within the meaning of Sec. 201(g)(1)(B) (21 U.S.C. 321(g)(1)(B)). Both courts held that they were not so used and therefore were not drugs.

It was also held below that "drug" must be limited to articles considered by the medical profession as drugs, since no other concept of the term was presented to Congress or described by Congress in the legislative record of the statute. The medical profession, as the testimony shows, regards as drugs only those articles which are administered to the patient or applied to the body in some way.

ARGUMENT

Introduction

The statement in the petition of the Question Presented (Pet. 2) is inaccurate and misleading.

Thus, to pose the question of whether sensitivity disks "containing various antibiotic drugs" are "antibiotic drugs" under the Act prejudges the very point which petitioner wants this Court to decide. The obvious and necessary implication is that the chemicals on the disks are drugs in some sense, presumably in the common understanding of that term, i.e. that they are medicines (Webster's International Dictionary). The implication is misleading. The chemicals are not available for use as drugs, not being in dosage form and being suitable only for use in laboratory testing procedures.

Moreover the fact that Bacto-Unidisks contain chemicals commonly used as drugs, i.e., antibiotic substances and sulfadiazine, has nothing to do with the question of whether the disk itself is a drug since, as the court of appeals recognized, it is the "intended use" of an article which determines whether it falls within the definition of "drug", i.e., whether it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease (Pet. 4a-5a).[1] Thus, neither the disk itself nor the

[1] As the court of appeals also noted (Pet. 4a), even honey may be a "drug" under the Act if it is intended for use in the treatment of disease within the meaning of Sec. 201(g)(1)(B); but

chemicals with which it is impregnated are drugs unless intended for such use.

The phrase in the Question Presented, "disks which physicians use [2] to select the antibiotic most appropriate to treat a particular patient"; being unqualified, conveys the idea that before an antibiotic is administered by the physician the disk indicates the proper drug to be used for the particular condition of the patient. This is not in accordance with the evidence. It is shown in the Argument that it is not the disk but the information derived from the entire testing procedure which may be used by the physician when he receives it—ordinarily some 24 to 36 hours or more after initial therapy has begun.

The Question Presented in the petition has been restated for the reasons set forth above.

A. The Alleged Public Health Need for Certification

1. The position of the Government as we understand it, is predicated squarely upon the proposition that sensitivity disks should be certified because, if they are not, the health of patients for whom antibiotic drugs are prescribed will be endangered and that, therefore, the definition of "drug" in the Act should be construed to include such disks.

The Government virtually ignores the testimony of the witnesses at the trial (both its own and those of respondent), presumably because that testimony contradicts its

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surely no rational person would suggest that its use in a laboratory testing procedure would constitute a use in the treatment of disease.

[2] This and other references in the petition to the use of the disk by the physician do not reflect the facts. The record clearly shows that the testing referred to is conducted by hospital and other laboratories and rarely by the physician himself. Dr. Keefer said, when asked whether it was "customary or rare" for practicing physicians to conduct sensitivity tests: "I would say from the total number of infections that doctors see and treat, both in their offices and in the home, and many in hospitals, the sensitivity test is not used. It is not used routinely" (R. 93a).

claim that the health of patients may be endangered by uncertified disks.

At the trial the Government attempted unsuccessfully, through two of its witnesses, to show such a public health need. Both admitted on cross-examination that they had not had any experience of harm occurring to a patient because of a sensitivity test using a faulty disk (R. 59a-60a, 64a, 102a).

Dr. Keefer testified affirmatively that he knew of no public health problem connected with the possible inadequacy of sensitivity disks (R. 95a), and that he had experienced no situation where the test was so inaccurate that it resulted in the administration of the wrong antibiotic "because in such instances where such a question may arise, the patient is usually getting one, two, three, and sometimes four antibiotics if he is desperately ill" (R. 96a).

In *United States* v. *Consolidated Laboratories, et al.* (Civil Action No. 63-C-23, D. Ill., March 29, 1963), also involving sensitivity disks, the Court found—

> "13a. There is no evidence of injury to the public from the use of the Multidisks" (160a).

The alleged element of hazard and claim of public health need for certification cannot, therefore, seriously be regarded as an issue in this case. The shallowness of the Government's claim is demonstrated by the fact that, had it been able to produce a witness at the trial to document the claim or even to testify to instances where (either before or after certification was instituted) faulty disks had affected the validity of a sensitivity test, it would surely have done so.

It is wholly unwarranted to state that "The need for assurance as to quality and potency is as great when the

antibiotic is used on a disc as when it is used in a pill or injection" (Pet. 14). It seems incredible that this Court would be asked to accept such a proposition in view of the testimony at the trial and the failure of the Government to produce any data to support its claim.

The fact that the Secretary's (Commissioner's) interpretation of the statute extending its coverage to sensitivity disks, was made in a rule-making proceeding, endows it with no aura of sanctity. The interpretation was just like any other statutory interpretation by an administrative official. Since, as the Court of Appeals said, it involved the question of whether the Bacto-Unidisk is within the jurisdiction of the Secretary under the Act, the decision was subject to reexamination by the courts. It is of interest to note also that the rule-making proceeding in question did not even involve the Bacto-Unidisk.[3]

In any event the "judgment" of the Secretary (Commissioner) upon which such great reliance is placed, was not supported by the evidence adduced at the trial of this case. There is no substance to the arguments advanced by the Government on this point.

2. The argument that the patient may be endangered if sensitivity disks are not certified is carried to the extreme of setting up the unfounded implication that the result of the sensitivity test is used as a guide to the *initial* selection by the physician of an antibiotic or antibiotics.[4] The fact is that, as all witnesses agreed, it is

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[3] The proceeding, and the regulation adopted pursuant thereto, applied to disks containing antibotic substances only and no other kind of chemicals (21 C.F.R. 147.2(a)). The Bacto-Undisk contains sulfadiazine, which is not an antibotic substance. Consequently it could not be certified, unless the combination on the disk of antibiotic substances with sulfadiazine were accepted by the Commissioner as "suitable" (21 C.F.R. 147.2(b)—"Packaging") and after regulations were adopted providing for that combination (21 C.F.R. 146.10).

[4] E.g., the phrase "discs which physicians use to select the antibiotic most appropriate to treat a particular patient" in the statement of the Question Presented, being unqualified, conveys the idea

the common practice for the physician to prescribe one or more antibiotics, on the basis of his clinical experience and information available to him from various sources, before the sensitivity test is run (Finding Number 8, R. 146a-147a; R. 43a, 52a-53a; 90a-91a; 104a).

Since the conditions for which antibiotic drugs are administered are infectious diseases, it is apparent that delay in institution of treatment would be undesirable.

The administration of antibiotics before the completion of the sensitivity test is ordinarily essential since from 24 to 36 hours, and sometimes more, may elapse before the sensitivity test is completed and the results are reported to the physician (assuming the physician has ordered a test at all). The preliminary test by which the organism in the specimen taken from the patient is isolated and identified involves 18 hours of incubation of a plated agar culture medium inoculated with a specimen,[5] and the subsequent sensitivity testing procedure usually requires an additional 18 hours incubation (Finding of Fact Number 7, R. 146a; R. 32a, 91a).[6]

Obviously, institution of treatment can rarely be delayed until completion of these tests. In this sense infections in which antibiotic therapy is indicated may involve

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that, before selection, a sensitivity test is run. The same implication is contained in the discussion on page 7. The correct statement would be, that, if the patient does not respond to the initial therapy, the results of the sensitivity test "might be used as an aid in changing or selecting another antibiotic" (R. 93a).

[5] The publication cited on page 6 of the petition (The Usefulness of In Vitro Sensitivity Tests in Antibotic Therapy, Annual Review of Medicine, Vol. 14, pp. 41-46 (1963)) states that the first principle upon which the rational use of antibiotic drugs should be based is that "the specific identity of the infecting organism must be determined" (p. 41). Dr. Truant testified that the identification procedure requires 18 hours (R. 32a).

[6] The 6 to 18 hours mentioned by Dr. Truant (R. 31a) and in the petition (p. 7) refer only to the sensitivity test itself which, in fact ordinarily takes substantially more than 6 hours (R. 16a, 32a, 91a).

emergency situations within the meaning of Finding of Fact Number 8. As Dr. Lerner, a witness for the Government put it, therapy is "almost always begun before the sensitivity test is completed" (R. 104a). As the court found, the results of the sensitivity test are later used by the physician to confirm his selection of an antibiotic (Finding Number 8, R. 147a).

The testimony and the findings of the district court obviously cannot be reconciled with the blanket statement in the petition (p. 10) that ". . . the labeling for most of the antibiotics available to prescribers tells the physician that his use of these drugs should depend upon the results of *in vitro* culture and sensitivity testing". The footnote (Number 3) to the quoted passage does not support it. The quotation from Physicians' Desk Reference (1968, p. 1173) refers to situations in which Lincocin is used as the sole antibiotic therapy. Obviously, if the patient were desperately ill the physician could not await the result of a sensitivity test to begin therapy with either Lincocin or one or more other antibiotics. Moreover, the footnote fails to indicate that in Supplement B to the 1968 Physicians' Desk Reference the product information has been revised to direct: "Do *in vitro* culture and susceptibility studies *in conjunction* with Lincocin therapy" (Supplement B 27, emphasis supplied). The statement as changed in the supplement is more consistent with medical practice as shown by the testimony at the trial.

B. The Statutory Definition of "Drug" As Applied by the Lower Courts

1. It is stated in the petition (p. 13) that "Despite a contrary suggestion by the court of appeals the discs are clearly used in the cure, mitigation, and treatment of disease". The statement will not stand examination. It is beyond cavil that the word "treatment" as used in Section 201(g)(1)(B) means "treatment of a patient". It seems quite obvious that a disk used only as a part of a test

procedure in a laboratory is not used in the treatment of a patient.

The Court of Appeals held that the Bacto-Unidisk "has nothing to do with the diagnosis or prevention of disease"; that "it is not intended for use either internally or externally to cure, mitigate, or treat disease"; and that "it only aids the physician to determine what antibiotics to use for the cure, mitigation or treatment of disease" (Pet. 3a).

This is in accordance with the evidence. It is clear that the *information* obtained from the *sensitivity test* (not just from the disk) is used as a guideline to treatment of some cases of disease (R. 33a-35a, 50a-51a, 90a-97a). The testimony fully supports the statement in Finding of Fact Number 8 (R. 146a-147a) that: "The information obtained from the sensitivity testing procedure outlined in Finding Number 7 is used by the physician as a guideline to treatment of the patient . . ."

No witness would accede to the Government's suggestions that the disk itself was used, or intended for use, in treatment[7] (E.g. Dr. Truant, R. 74a-75a). When therefore, the Petition refers to disks as "the means of determining which of such drugs [antibiotics] to administer to the patient" (p. 11) it is plainly inaccurate. Indeed, Finding of Fact Number 8 (R. 146a-147a) makes it clear, with respect to the information obtained from the sensitivity test that: "The disk, the culture medium, the Petri plate, and the incubation are all a part of the testing procedure yielding this information"; that "such information could not be obtained from the disk itself"; and that "the test is only one of many sources (such as the physicians experience, clinical symptoms, the litera-

[7] The Government largely abandoned its contention that the disk was used in diagnosis (R. 26a-27a), and does not press it here. The disease cannot be diagnosed (or recognized, R. 88a) until the suspected organism has been identified, and the sensitivity test does not enable one to identify an organism (R. 88a-89a).

ture, and other tests such as urinalysis and blood serum tests) of the information upon which the physician relies in determining the treatment to be administered". It is thus apparent that if the disk is a "drug", so are the culture medium, the Petri plate, and the incubator, as well as the medical literature and materials used in other tests such as urinalysis and blood serum tests (and others employing body specimens).

The District Court found that—

> "In medical science those substances which are for administration to or for use on, a person for the treatment of disease or injury, are regarded as drugs (Tr. 102-103, 195, 199, 261-262, 283). This is the commonly accepted view of physicians generally. A physician who testified for the libelant could think of no example of a substance not taken into or applied to the body which he would 'consider medically' as a drug (Tr. 103)". (Finding Number 9, R. 147a).

The Court also found that "The article does not purport to be and is not represented as a 'drug' as that term is used in medical science or by physicians generally. It is labeled 'For Laboratory Use . . .'". (Finding of Fact Number 11, R. 148a).

These findings are fully supported by the record and are not challenged by the Government. They lend powerful support to the clear purport of the testimony that the disk is not used in the treatment of disease but that the information obtained from the sensitivity test (in which the disk is used) is a guideline to therapy which becomes available some 24 to 36 hours after initial therapy has begun.

The petition offers no standard for determining the scope of the definition of "drug" as an alternative to that of the concept of the term in medical science. The only other available test for applying the definition therefore is that of whether, in the view of the Food and Drug Administration, a given article should be controlled under

the Act. This is neither an orderly nor a reasonable way of determining the coverage of a statute.

The Bacto-Unidisk is a laboratory reagent. There are more than 150 pages in the United States Pharmacopeia (and others in the National Formulary) describing hundreds of laboratory reagents or testing materials for use in making the various tests and assays described in the Pharmacopeia.[8] If the Government's position that sensitivity disks are used in the treatment of disease were sound, the Food and Drug Administration could, on the basis of the same approach, classify many, and perhaps most, of those reagents as "drugs" under the statute.

There is absolutely no warrant for the extension of jurisdiction over these laboratory tools, either in the statute or its legislative history. The proper forum for the Administration to advocate the subjection of sensitivity disks to the Act is the Congress. If the Administration can present a serious basis for statutory coverage of disks it will, as it has heretofore, receive the attention of the national legislature. Instead, during the six years of this litigation, the spectre of danger to health has been repeatedly flaunted without the production of any data to support it.

Finally, if the Government's position were sound the disk could legally be represented in its labeling as suitable for the treatment of disease; for example, "for use in the treatment of bacterial infections". Such a statement would obviously be false and would constitute misbranding under Section 502(a) of the Act (21 U.S.C. 352(a)), which deems a drug to be misbranded "if its labeling is false or misleading in any particular."

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[8] These reagents are not regarded as drugs by the Committees on Revision of the official compendia (Sec. 201(j), 21 U.S.C. 321(j)) and therefore do not appear in the monograph section of the compendia. Thus, they are not "recognized" in the sense of Sec. 201(g)(1)(A). (R. 112a-113a; 115a-117a; 127a-132a).

2. The Courts below did not, as suggested by petitioner (Pet. 12), disregard principles of statutory interpretation set forth by this Court. The statute does contain its own definition of "drug", thereby making that word a term of art (Pet. 13, Note 5). The applicable portion of the definition is, however, composed of words having a technical meaning, i.e., "diagnosis, cure, mitigation, treatment or prevention of disease." Recognizing this fact, *both petitioner and respondent* presented evidence by distinguished medical and scientific witnesses as to the meaning of the word "drug" in terms of the statutory definition, and its application to sensitivity disks. In receiving such evidence, the trial court was following a long-established principle of statutory construction set forth by this Court in a number of cases, *viz.*, resort to expert evidence *aliunde* in order to give meaning to technical statutory language. *Binns et al.* v. *Lawrence*, 53 U.S. 9; *Boston Sand & Gravel Co.* v. *United States*, 278 U.S. 41; *National Labor Relations Board* v. *Coca-Cola Bottling Co.*, 350 U.S. 264.

The Tariff Act of 1846 contained certain technical words descriptive of the shape of glass, e.g., "not cut or moulded". In *Binns*, *supra*, the Court held that the testimony of glass manufacturers at trial as to the meaning of those terms was controlling in applying the provisions of the Tariff Act, stating in part:

> "Where a statute may be ambiguous in its language, or may have reference to facts or conclusions dependent on usage, the influence of opinion or the proof of established usage may be proper or even indispensable, in fixing the just interpretation of the law . . ." 53 U.S. at 18-19.

On this point, Mr. Justice Holmes states in his opinion in *Boston Sand and Gravel*, *supra*:

> "It is said that when the meaning of language is plain, we are not to resort to evidence in order to raise doubts. That is rather an axiom of experience

> than a rule of law, and does not preclude consideration of persuasive evidence if it exists." 278 U.S. at 48.

In a more recent decision this Court reaffirmed the principle that technical words must be given their technical meaning rather than their common, everyday meaning, citing *Boston Sand & Gravel*:

> "If the word be deemed to have a peculiar connotation for those intimate with trade-union affairs, it is incumbent upon us to give the word its technical meaning . . ." *National Labor Relations Board* v. *Coca-Cola Bottling Co.*, 350 U.S. 264, 269.

It is thus clear that the courts below did not disregard principles of statutory construction enunciated by this court. Indeed, petitioner itself agreed at trial that the experts were of help to the Court in this matter (R. 76a). Petitioner cannot now ignore the testimony of its witnesses and respondent's as to the meaning of the word "drug" and urge that because of danger to public health (unsupported by even its own witnesses) sensitivity disks should be classified as drugs.

Securities and Exchange Commission v. *Ralston Purina Co.*, 346 U.S. 119 (Petition 12) is inapposite. There, the offering of securities with respect to which no registration statement was in effect was clearly within the statutory prohibition *unless* it was exempt as "not involving any public offering". The Court, following established principles, placed upon the issuer of the securities the burden of proof of showing that the offering fell within the exemption. The issuer was unable to meet the burden. Here, in contrast, the burden of proof was upon the government to establish that Bacto-Unidisks were "drugs". It failed to do this and now offers its unsupported public health argument as a basis for overturning the findings and decisions of the lower courts.

C. *AMP, Inc.* v. *Gardner*

Petitioner states (Pet. 15) that in *AMP, Inc.* v. *Gardner*, 389 F. 2d 825, 830 (C.A. 2), pending on petition for certiorari No. 86, the Second Circuit rejected the idea that the statute was "restricted to products commonly called 'drugs'", citing also *Bradley* v. *United States*, 264 Fed. 79 (1920), which arose under the Food and Drugs Act of 1906.

The purpose of noting here that the Act is not restricted to products commonly called drugs or to dictionary or pharmacopeia definitions is obscure, since nobody to our knowledge disputes the proposition that it is the "intended use" of the product which determines whether it is a drug (i.e., whether it is for use in the diagnosis or treatment of disease) and the Court of Appeals specifically recognized that principle in the instant case. (Petition 4a-5a). That is why spring water is a "drug" if it is recommended for use in the treatment of disease. (*Bradley* v. *United States*, *supra*).

In its Brief in Opposition to the Petition for Certiorari in *AMP* the Government states with respect to the suture material there involved (p. 7):

> "The essential element, nylon suture material, is recognized as a drug in the official United States Pharmacopeia and therefore is squarely within that portion of the statutory definition which defines as drugs 'articles recognized in the Official United States Pharmacopeia.' Cf. *United States* v. *48 Dozen Packages . . . of Gauze Bandage*, 94 F.2d 641 (C.A. 2)".[9]

In the instant Bacto-Unidisk case the Courts concluded that the disks were not used in the diagnosis or treatment of disease and were therefore not "drugs"; and

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[9] The Gauze Bandage case suggests, and it is our view, that since articles such as sensitivity disks are not "recognized" in an official compendium they are not "of a kind" with the articles which are so recognized and that, therefore, the doctrine of *ejusdem generis* applies to exclude such disks from the definition of "drug".

that, moreover, only substances administered to patients or applied to the body or intended for such use were "drugs". The Brief in Opposition in *AMP* (pp. 8-9) notes that, unlike the disks, the article there involved enters the surgical wound and part of it remains in the body. It also points out (p. 7) that the article is used to ligate or tie off bleeding blood vessels during a surgical operation and that, therefore, it affects the structure or function of the body within the meaning of Section 201(g)(1)(C).

It is fully apparent therefore that there are both legal and factual differences between the instant case and *AMP*, and the Government so states in its Brief in Opposition in *AMP* (pp. 8-9). Even more conclusive, however, is the fact that Petitioner AMP, Inc., unlike Difco Laboratories, did not dispute the proposition that its product was subject to the Act (either as a drug or as a device) and, in the language of the court of appeals, "proceeded to comply with the requirements of the Act relating to devices" (389 F.2d at 826).

AMP, Inc. conceded, therefore, that its product was "intended for use in the diagnosis, cure, mitigation or treatment of disease" or "intended to affect the structure or function of the body", or both, since it would not be a device under Section 201(h) unless it was intended for one or more of such uses. The language relating to diagnosis and treatment (Section 201(h)(1)) and that relating to effect upon the structure or function of the body (Section 201(h)(2)) are common to the definitions of "drug" and "device". The very question in the Bacto-Unidisk case is whether the disk falls within the provision of Section 201(g)(1) which corresponds to Section 201(h)(1), *viz.*, Section 201(g)(1)(B), relating to diagnosis and treatment.

It is obvious, therefore, that the "broad construction" given to the Act in *AMP* is not comparable to that which the Government is seeking with respect to Bacto-Unidisks.

In the former the basic jurisdictional test was concededly met and the question was only one of classification as between "drug" and "device". In the latter the testimony at the trial shows that the basic jurisdictional test, *viz.*, whether the disk is used in the diagnosis or treatment of disease, is not met. In addition, the possible dangers involved in permanent incorporation of a substance into the human body are obviously not present in the case at bar.

D. The Inapplicability of the Certification Provisions (Sec. 507) to Articles Not Administered or Applied to Patients

The petition correctly states that the provision for the certification of antibiotic drugs (Sec. 507, 21 U.S.C. 357) was adopted in order "to adequately insure safety and efficacy of use." Petitioner fails to point out, however, that (1) when Section 507 was enacted in 1945 no antibiotic sensitivity disks were being produced commercially and Congress had never heard of such articles, (2) the language of Section 507 and the applicable legislative history clearly show that the concern of FDA and Congress was to protect patients from the administration of an antibiotic drug (penicillin) which was not safe and efficacious for its intended use.[10] Antibiotic drugs other than penicillin were brought under certification in 1947 and 1949, but there was no deviation from the concept that the purpose of certification was to protect patients to whom such drugs were administered.[11]

In a letter to the President of the Senate the Federal Security Administrator[12] said that the drugs being added to the certifiable list were "highly efficacious for one or more serious diseases", such as rickettsial diseases,

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[10] S. Rep. No. 410 and H. Rep. No. 702, 79th Cong., 1st Sess (1945).

[11] E.g., S. Rep. No. 600, 81st Cong. 1st Sess., (1949), 1949 U.S. Code Congressional Service at 1530-1531.

[12] The predecessor of the Secretary of Health, Education and Welfare.

atypical pneumonia, and virus diseases.[13] Obviously the Administrator was talking about drugs to be used for administration to patients.

In 1962 Section 507 was amended to extend certification to all antibiotics "intended for use by man" (as distinguished from veterinary use).[14]

The words "intended for use by man" and "for human use" are used interchangeably throughout the several committee reports on the bills which became the Drug Amendments of 1962.[15] In the context, they quite clearly refer to use for administration to man by ingestion or otherwise. Thus, the uses of sensitivity disks are clearly excluded, whether the organism being tested by the disk is from man or animal.

The Department of Health, Education and Welfare, under date of October 10, 1962, released a document entitled, "Drug Amendments of 1962, Federal Food, Drug and Cosmetic Act—Summary", which is explicit. It states under "Batch Certification of Antibiotics" that:

> "14. All antibiotic drugs to be *administered to humans* are made subject to batch-by-batch testing and certification by FDA for identity, strength, quality, and purity to assure that they "are safe and effective before they are released for sale." [Emphasis supplied].[16]

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[13] Op. cit. supra., S. Rep. No. 600, U.S. Code Congressional Service at 1531, 1532.

[14] Drug Amendments of 1962, P.L. 87-781, 76 Stat. 780, Sec. 105(a), amending Section 507(a).

[15] S. Rep. No. 1744, Parts I (July 19, 1962) and 2 (August 21, 1962), 87th Cong. 2d Sess., on S. 1552, p. 19 (Part I) and p. 9 (Part 2); H.R. Rep. No. 2464, 87th Cong., 2nd Sess., p. 11 (1962); H.R. Conference Report No. 2526, 87th Cong., 2d Sess., on S. 1552, p. 21 (1962). Part I of the Senate Report and the Conference Report are set out in U.S. Code Congressional and Administrative News, Vol. 2, 1962, at pp. 2884 and 2927.

[16] A subsequently issued printed pamphlet entitled "Summary of the Drug Amendments of 1962" repeats this statement on page 6.

Sensitivity disks, of course, are not "administered" at all. It is evident, therefore, that the Congress, in extending certification authority in the 1962 amendments, and limiting it to antibiotics administered to human beings, was following the pattern established by Section 507 as originally enacted and as reflected in its legislative history.

Moreover, it seems quite clear that the concept of "safety of use" is applicable only to dosage forms of substances which are administered to patients. This is the clear pattern of the statute. Thus, "safety of use" is a statutory test of pre-marketing clearance of a "new drug" under Section 505 of the Act (21 U.S.C. 355). It clearly refers to safety for application or administration to patients.[17]

The concept of safety of use is inapplicable to sensitivity disks, since they are not applied or administered to the patient. It seems clear, therefore, that, even if they were drugs, they would not be subject to certification under Sec. 507.

E. The Bacto-Unidisk as a Device

The suggestion was offered to the lower courts on behalf of respondent that, if the Bacto-Unidisk were subject to the Act at all (respondent contends it is not), it should be treated as a device within the meaning of Sec. 201(h) (21 U.S.C. 321(h)). As a device it would not be certifiable.

The only difference between a drug and a device insofar as the definition of "device" and the pertinent portion of the definition of "drug" (Section 201(g)(1)(B)),

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[17] See, e.g., Report of Special Committee to Review the Policies, Procedures, and Decisions of the Division of Antibiotics and the New Drug Branch of the Food and Drug Administration (approved September 27, 1960); and analysis of H.R. 11581, 87th Cong., 2d Sess., by Department of Health, Education and Welfare, Hearings before the Committee on Interstate and Foreign Commerce, House of Representatives, 87th Cong., 2d Sess., on H.R. 11581 and H.R. 11582 (p. 23).

are concerned, is that devices are "instruments, apparatus and contrivances" and drugs are articles other than instruments, apparatus, and contrivances.[18]

Sensitivity disks are logically classified as "instruments, apparatus, or contrivances," if, contrary to our view, they are to be regarded as used in the "diagnosis, cure, mitigation, treatment, or prevention of disease" or "to affect the structure or any function of the body." As the testimony shows, there is nothing in the nature or manner of use of reagent disks to justify their classification as drugs. It is less difficult to conceive of them as "devices" (assuming that they are subject to the act at all) because they are in fact a "means" or "appliance" within the dictionary definition of the term.[19]

A "generator" supplying chlorine gas for *inhalation* by patients to treat arthritis and sinusitis was considered by the Food and Drug Administration and treated by the Court as a "device" in *United States* v. *22 Devices . . . Halox Therapeutic Generator*, 98 F. Supp. 914 (D. Cal. 1951).

A so-called cancer diagnosis kit with two bottles of common chemicals (one of which was ether, a substance commonly used as a drug), which were to be added to a sample of the patients urine to determine whether cancer was present, was considered to be a "device" and an injunction was granted against its shipment.[20] Likewise, a

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[18] The last clause of Section 201(g)(1) expressly provides that the definition of "drug" does not include devices.

[19] The pertinent definitions in Webster's New International Dictionary are as follows: Device: "1. That which is devised, or formed by design; a contrivance; an invention. . ." Instrument: "1. That by means of which any work is performed or result is effected; a medium; means." Apparatus: ". . . Specif. Any complex instrument or appliance, mechanical or chemical, for a specific action or operation. . ." Contrivance: ". . . 3. A mechanical device; an appliance."

[20] Annual Report of the Food and Drug Administration, 1955, Kleinfeld & Dunn, Federal Food, Drug and Cosmetic Act, 1953-1957, p. 650.

radio diagnostic and treatment machine which was held forth as requiring only a drop of the patient's blood for diagnosis and treatment of various disease conditions, was considered by FDA as a "device", not a drug. The device was seized and a criminal prosecution was brought against its shipper.[21]

It seems manifest that if the disks are drugs because their use involves the testing of organisms from the patient as an aid in deciding upon the proper treatment, the last two devices above described likewise fall into that category. In fact, however, it seems clear that none of the three articles is a drug.

It is useful to recall at this juncture that sensitivity disks are used neither to diagnose a disease or to treat or prevent it. The information derived from them is at most an aid in determining whether the initial therapy should be continued. The disks are therefore distinguishable even from the alleged uses of the devices which have been described.

CONCLUSION

The basis for the Government's position is the proposition that the public health may be endangered if sensitivity disks are uncertified and that, therefore, the definition of "drug" should be interpreted to include such disks. It has been shown that the record fails to support the danger-to-health thesis; that, on the contrary, the testimony contradicts it affirmatively. Consequently, the Government is left only with the question of whether the definition of "drug" may reasonably be construed to apply to sensitivity disks. The only ground for such an inter-

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[21] Annual Report, Food and Drug Administration, 1950, Kleinfeld & Dunn, Federal Food, Drug and Cosmetic Act, 1953-1957, pp. 575, 624. To the same effect is Notice of Judgment under Federal Food, Drug and Cosmetic Act, no. 4667 (Injunction against the device, D. Calif., 1956).

pretation would be that the disk is used, or intended for use, in the treatment of disease. Logic, the expert testimony, and the findings of the district court show that it is not so used or intended; that its use is as a part of a laboratory testing procedure yielding information which may be used by physicians as a guideline to the changing or selection of an appropriate antibiotic drug to treat patients who have not responded to initial therapy.

For the reasons stated, it is respectfully submitted therefore that the decisions below were clearly correct and that the petition for a writ of certiorari should be denied.

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In the Supreme Court of the United States

OCTOBER TERM, 1968

No. 343

UNITED STATES OF AMERICA, PETITIONER

v.

AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * *

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT

REPLY MEMORANDUM FOR THE PETITIONER

Respondent asserts that there is no danger to health from uncertified antibiotic discs, and that the government's witnesses contradicted any claim that patient health might be endangered (Br. in Opp. 3, 5–6).

1. It is undisputed that the results of sensitivity testing with antibiotic discs, such as the Bacto-Unidisk, frequently lead physicians to change from one antibiotic that has been used to initiate therapy to another antibiotic shown by sensitivity testing to be more effective in combating patients' infections. Indeed, Dr. Keefer, respondent's medical witness, said that disc sensitivity testing "is usually employed in patients who have infections—complicated infections—such as urinary tract infections, who are not

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responding to a broad spectrum antibiotic", with the result that "the treatment is frequently changed" (R. 93a).

2. Respondent is in error in stating that two government witnesses were unable to support the proposition that certification of sensitivity discs is needed to avoid a danger to the health of patients (Br. in Opp. 3, 6).

On the very pages of the record it cites (R. 59a, 60a, 64a, and 102a), Dr. Truant testified: that "false readings" would be obtained from improperly prepared discs and that the physician consequently "would not treat the patient properly" (R. 59a); that poor standardization would result in production of discs "of poor quality, which would give misinformation" to the laboratory and the clinician (R. 60a); and that while he could not put his finger on a specific example in which a physician had been misled to the detriment of a patient, he could "recall that there were a number of instances brought to my attention by individuals in the infectious disease department" (R. 64a).

Dr. Lerner was asked on cross-examination whether he thought "the public health was involved" in disc reliability. He replied that he did (R. 102a). While he personally had not seen a case of patient harm from a faulty disc, he had on some occasions discarded disc data as unreliable because it was inconsistent with other information concerning the patient's condition (R. 102a). On the preceding page, not cited by respondent, Dr. Lerner was asked on direct examination about the importance of disc standardization

and reliability. He answered, "I feel that it is vital" (R. 101a). Hospital laboratories, he said, were unable to check discs for performance, and thus had to rely upon the label representations as to their composition and their performance (R. 100a–101a).

3. This record thus confirms the administrative determination that sensitivity disc reliability is essential to the safe and effective use of antibiotic drugs and our contention that antibiotic certification requirements were properly applied to such discs to assure their reliability, after numerous complaints and an extensive administrative investigation (see Pet. 7–8). There was ample basis developed in the rule-making proceedings for the administrative determination that results yielded by a sensitivity test with a disc impregnated with an improper amount of an antibiotic drug, or with a disc which does not properly diffuse its antibiotic drugs into the bacterial growth media, pose a real danger of improper and ineffective therapy with the wrong drug at a critical stage of the patient's course of treatment. As our petition shows, the antibiotic certification procedures were designed to assure the quality and performance characteristics needed to prevent such therapeutic misadventures. The correctness of the decision of the court of appeals, which bars this vital protection for the public health, presents an important question of statutory interpretation warranting review.

Respectfully submitted.

ERWIN N. GRISWOLD,
Solicitor General.

OCTOBER 1968.

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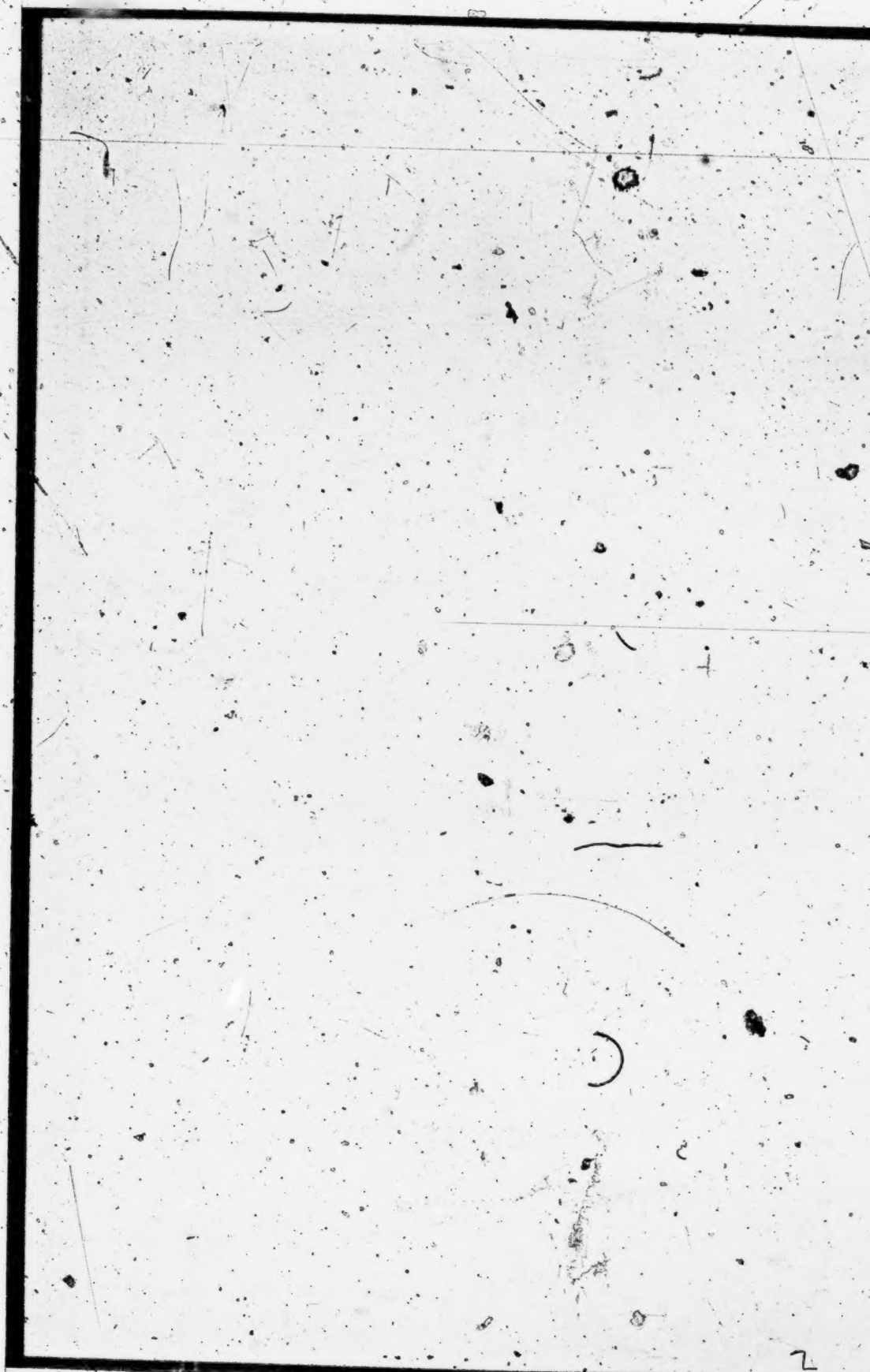

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IN THE

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OCTOBER TERM, 1968

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Petitioner,

v.

AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * *

PETITION OF CLAIMANT DIFCO LABORATORIES, INC. FOR REHEARING OF ORDER GRANTING PETITION FOR WRIT OF CERTIORARI

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AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * *

PETITION OF CLAIMANT DIFCO LABORATORIES, INC. FOR REHEARING OF ORDER GRANTING PETITION FOR WRIT OF CERTIORARI

Respondent petitions this Court for rehearing of its order of October 21, 1968 granting the petition of the Government for a writ of certiorari to review the judgment of the United States Court of Appeals for the Sixth Circuit herein, and, upon such rehearing, for denial of the writ.

REASONS FOR GRANTING REHEARING AND DENYING THE WRIT

Since the Brief of Claimant Difco Laboratories in Opposition was filed in the instant Bacto-Unidisk case this Court, on October 14, 1968, denied the petition for a writ of certiorari in *AMP Incorporated* v. *Cohen*, No. 86, this term. Following the granting of the petition for a writ in the instant case, petitioner in *AMP* filed a Petition for Rehearing of the order denying its petition, stat-

ing in part as grounds therefor that this Court in the case at bar will be deciding the same issues as presented in *AMP*. On the other hand, the Government in its Brief in Opposition to the *AMP* petition had stated that the decision of the Court of Appeals for the Sixth Circuit in the instant case was not in conflict with the decision of the Appellate Court in *AMP* and that "whether or not the Sixth Circuit decision is correct, the case differs from the present one both factually and legally" (Brief in Opposition, 8-9). We agree with that statement of the Government. The Government, nevertheless, in its petition for a writ of certiorari in the instant case, contended that the Sixth Circuit decision represents "a conflicting approach to the interpretation of the Act" (Pet. 15). It is submitted that, in view of the denial of the petition in *AMP* and the conflicting views with respect to the instant case stated by petitioner in *AMP*, by the Government, and by this respondent, the differences of law and fact involved in the two cases should be clearly delineated for this Court as set forth below. We believe that such a delineation should lead this Court to grant a rehearing in the case at bar and to deny the Government's petition for a writ of certiorari.

1. The articles involved in the two cases are of entirely different kinds and the portions of the definitions of "drug" and "device" relating to the structure or function of the body (Sections 201(g)(1)(c) and 201(h)(2) of the Act), which are pertinent in *AMP*, are not applicable in any way in the Bacto-Unidisk case. It is clear from the testimony of the witnesses for both the Government and the respondent that the Bacto-Unidisk is used in the laboratory only and not in the "treatment of disease" within the meaning of Section 201(g)(1)(B), the only portion of the definition of "drug" which the Government seriously contends is applicable.* The disk,

* The original Government position that the disks were used in diagnosis and prevention was not pressed in the Court of Appeals. It is untenable.

therefore, satisfies no jurisdictional requirement of the definition of "drug" under Section 201(g)(1) of the Act. *AMP*, on the other hand, involves appliances which are used to ligate or tie off bleeding blood vessels during a surgical operation and which therefore affect the structure or function of the body within the meaning of Section 201(g)(1)(c) or 201(h)(2). The Government so noted in its Brief in Opposition in that case (p. 7). Moreover, nylon suture material is "recognized" in the United States Pharmacopeia and sensitivity disks are not.

No witness either for the Government or respondent would accede to the Government's suggestion that the Bacto-Unidisk was used in the treatment of disease (e.g., Dr. Truant, a witness for the Government, R. 74a-76a). Finding No. 8 (R. 146a-147a) states that "the information obtained from the sensitivity testing procedure outlined in Finding Number 7 is used by the physician as a guideline to treatment of the patient . . .". Since all witnesses agreed, there is no basis for disturbing this finding. It follows that no amount of argument can bring the Bacto-Unidisk into the scope of the definition of "drug" under the statute and that, therefore, there is no occasion for consideration of this case by this Court. It seems obvious that the issues in the Bacto-Unidisk case and those in *AMP* are entirely different.

2. The decision in *AMP* is not "principally relied on" by the United States in its petition in the Bacto-Unidisk case, as stated in the Petition for Rehearing in *AMP Incorporated* v. *Cohen* (p. 2).

On the contrary, both the petition of the Government in the Bacto-Unidisk case and the Reply Memorandum for the Petitioner therein seek primarily to persuade this Court to disregard the findings of fact and decisions below and to expand judicially the statutory definition of drug on the ground that, otherwise, harm may come to some patients by reason of the use of faulty sensitivity disks—despite the fact that no data showing even one in-

stance of such an occurrence could be produced at the trial by any Government witness.

The Government did state, in its petition, that *AMP* and other cases cited were in conflict with the Bacto-Unidisk decision because they rejected "common usage as determinative of what constitutes a drug" (p. 15).

The Bacto-Unidisk decisions did not, however, turn upon "common usage" as to what is a drug. The term "treatment of disease" in the definition of "drug" is a term of technical significance in medical science and was so treated by the Courts below and the parties, both of whom presented expert testimony as to its meaning. This was proper. *United States* v. *American Trucking Associations*, 310 U.S. 534, 543-544 (1940); *St. Luke's Hosp. Assoc. of Cleveland, Ohio* v. *United States*, 333 F. 2d 157 (6th Cir., 1964); Wigmore on Evidence, Vol. VII, Sections 1918, 1923, 1955, pp. 11, 21, 85. This testimony, and that relating to the meaning of the term "drug" did not deal with "common usage" but with the meaning of medical terms to medical doctors. Moreover, although it is not used in or on the body and is therefore not a drug in the *medical sense* (Finding No. 9, R. 147a), the Bacto-Unidisk would be a drug in the *statutory sense* if it purported to be or were represented to be for the treatment of disease (as the District Court found it was not, Finding No. 11, R. 148a), despite the fact that it could not be so classified on the basis of "common usage".

Obviously, therefore (a) the decisions below in *AMP* were not "principally relied on" by the Government in its Bacto-Unidisk petition and (b) to the extent there was reliance upon the *AMP* decisions it was misplaced.

It is submitted, therefore, that this case presents no material question of law or fact to this Court while *AMP* presents a substantial question of law. It is suggested further that the decision in *AMP* has no material relevance to the instant case because of the clear legal and factual differences herein set forth.

For these reasons and those stated in the Brief of Claimant Difco Laboratories, Inc. in Opposition we urge that rehearing be granted and that, thereupon, the petition for writ of certiorari to the United States Court of Appeals for the Sixth Circuit be denied.

Respectfully submitted,

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Of Counsel:

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CERTIFICATE OF COUNSEL

I hereby certify that the foregoing petition for rehearing is presented in good faith and not for delay and is restricted to grounds specified in Rule 58 of the rules of this Court.

EDWARD BROWN WILLIAMS
Counsel for Difco Laboratories, Inc.

November 1968

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In the Supreme Court of the United States

OCTOBER TERM, 1968

No. 343

UNITED STATES OF AMERICA, PETITIONER

v.

AN ARTICLE OF DRUG * * * BACTO UNIDISK * * *

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT

BRIEF FOR THE UNITED STATES

OPINIONS BELOW

The opinion of the court of appeals (App. 198–202) is reported at 392 F. 2d 21. The opinion of the district court (App. 186–191) is not reported.

JURISDICTION

The judgment of the court of appeals was entered on March 29, 1968 (App. 203). On June 18, 1968, Mr. Justice Stewart extended the time for filing a petition for a writ of certiorari to and including July 26, 1968 (App. 204). The petition was filed on that date, and was granted on October 21, 1968 (App. 206). The jurisdiction of this Court rests on 28 U.S.C. 1254(1).

QUESTION PRESENTED

Whether the Secretary of Health, Education, and Welfare correctly concluded that discs containing various antibiotic drugs—discs which physicians use to select the antibiotic most appropriate to treat a particular patient—are "antibiotic drugs" under the Federal Food, Drug, and Cosmetic Act, and therefore are subject to the requirement in Section 507 of that Act that, pursuant to regulations of the Secretary, each such drug be tested by batches to insure its safety and efficacy.

STATUTE INVOLVED

The Federal Food, Drug, and Cosmetic Act, 52 Stat. 1040 (1938), as amended, 21 U.S.C. 301, *et seq.*, provides in part:

> *Sec. 201* [*21 U.S.C. (Supp. II) 321*]
>
> For the purposes of this Act—
>
> * * * * *
>
> (g) (1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C); but does

not include devices or their components, parts or accessories.

* * * * * * *

(h) The term "device" * * * means instruments, apparatus, and contrivances, including their components, parts, and accessories, intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; or (2) to affect the structure or any function of the body of man or other animals.

Section 502 [*21 U.S.C. 352*]

A drug or device shall be deemed to be misbranded—

(l) If it is, or purports to be, or is represented as a drug composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other antibiotic drug, or any derivative thereof, unless (1) it is from a batch with respect to which a certificate or release has been issued pursuant to section 507, and (2) such certificate or release is in effect with respect to such drug: *Provided,* that this paragraph shall not apply to any drug or class of drugs exempted by regulations promulgated under section 507 (c) or (d).

Section 507 [*21 U.S.C. 357*]

(a) The Secretary of Health, Education, and Welfare, pursuant to regulations promulgated by him, shall provide for the certification of batches of drugs composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other antibiotic drug, or any derivative thereof.

A batch of any such drug shall be certified if such drug has such characteristics of identity and such batch has such characteristics of strength, quality, and purity, as the Secretary prescribes in such regulations as necessary to adequately insure safety and efficacy of use, but shall not otherwise be certified. Prior to the effective date of such regulations the Secretary, in lieu of certification, shall issue a release for any batch which, in his judgment, may be released without risk as to the safety and efficacy of its use. Such release shall prescribe the date of its expiration and other conditions under which it shall cease to be effective as to such batch and as to portions thereof. For purposes of this section and of section 502(*l*), the term "antibiotic drug" means any drug intended for use by man [1] containing any quantity of any chemical substance which is produced by a microorganism and which has the capacity to inhibit or destroy microorganisms in dilute solution (including the chemically synthesized equivalent of any such substance).

(b) Regulations providing for such certifications shall contain such provisions as are necessary to carry out the purposes of this section, including provisions prescribing (1) standards of identity and of strength, quality, and purity; (2) tests and methods of assay to determine compliance with such standards; (3) effective

[1] This definition was added by the Drug Amendments of 1962, P.L. 87-781, 76 Stat. 785, to extend the certification controls to all antibiotics intended for human use, as contrasted with drugs solely for veterinary use. H. Rep. 2526, 87th Cong., 2d Sess., October 3, 1962, Conference Report, Statement of Managers on the Part of the House, pp. 21-22; S. Rep. 1744, 87th Cong., 2d Sess., p. 19. See also the Statement by Senator Kefauver, 103 Cong. Rec. 22039, October 3, 1962.

periods for certificates, and other conditions under which they shall cease to be effective as to certified batches and as to portions thereof; (4) administration and procedure; and (5) such fees, specified in such regulations, as are necessary to provide, equip, and maintain an adequate certification service. Such regulations shall prescribe only such tests and methods of assay as will provide for certification or rejection within the shortest time consistent with the purposes of this section.

STATEMENT

On May 25, 1962, the United States District Court for the Eastern District of Michigan ordered the seizure of an interstate shipment of five cases of articles labeled "Bacto-Unidisk" pursuant to a libel filed by the government charging that the articles were composed of antibiotic drugs which were neither certified nor exempted from certification as required by Section 507 of the Federal Food, Drug, and Cosmetic Act, *supra*, and the regulations issued thereunder (21 C.F.R. 147) (App. 5–6). On August 21, 1966, after a trial, the court ruled that the articles were not "drugs" within the meaning of the statute and ordered them returned to the claimant, Difco Laboratories (App. 192–196). The court of appeals affirmed (App. 198–203).

1. BACKGROUND[2]

Antibiotics are chemical substances, produced by various species of microorganisms, which suppress the

[2] In addition to the materials cited therein, the text is derived from Bauer, Kirby, Sherris, and Turck, *Antibiotic Susceptibility Testing by a Standardized Single Disk Method*, 45 American Journal of Clinical Pathology 493, at 493–494, 496 (1966);

growth of other microorganisms and may eventually destroy them. The systematic use of antibiotics as therapeutic agents began in the early 1940's with the advent of penicillin. When of proper potency and free from toxic impurities, penicillin proved useful for treatment of numerous life-threatening infectious diseases. Penicillin was produced by a biological process, however, and was subject to the vagaries inherent in such processes. Moreover, the methods for assaying the potency of penicillin were also biological in nature, and were generally uncertain and variable unless conducted under very carefully controlled conditions. Because of this, and because methods previously developed to assure quality control in the preparation of other drugs were inadequate to deal with a substance having these characteristics, Congress, in Section 507 of the Act, *supra*, directed the Secretary of Health, Education and Welfare to promulgate regulations establishing such standards of identity, potency, quality and purity as are necessary to insure the safety and efficacy of antibiotics for their intended use, and to provide for the certification of batches meeting such standards. See H. Rep. 702, 79th Cong., 1st Sess. (1945), particularly the letter from the Acting Federal

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Petersdorf and Sherris, *Methods and Significance of in Vitro Testing of Bacterial Sensitivity to Drugs*, 39 American Journal of Medicine 766, at 771 (1965); Gould, *The Laboratory Control of Antibiotic Therapy*, 3 Chemotherapia 477, at 478–481 (1961); Second Report of the Export Committee on Antibiotics, *Standardization of Methods for Conducting Microbic Sensitivity Tests*, World Health Organization Technical Report Series No. 210, pp. 12–17 (1961).

Security Administrator recommending the legislation, pp. 10–11.

More than 30 antibiotics are currently listed (21 C.F.R. 145.3). The regulations governing these various antibiotics now cover more than 700 pages in the Code of Federal Regulations, consisting for the most part of highly detailed specifications and standards designed to assure the safety and efficacy of each of the antibiotics in each of its various forms (21 C.F.R. 141.1–148z.4).

With the development of the many forms of antibiotics (including some which present a serious risk of undersirable and sometimes dangerous side effects, when administered to some patients), it became important in medical practice to have a screening test which would provide the physician with an accurate estimate as to which among the several available antibiotics would be likely to be effective against his patient's infecting organism. A diffusion test, using antibiotic sensitivity discs, soon became the most widely employed screening method. In this test, a specimen of the affected fluid (blood, spinal fluid, sputum, urine, pus, etc.) is drawn from the patient. The specimen is applied upon an agar culture medium contained in a small glass dish, and is incubated for a period of hours. Sample cultures (isolates) of the infecting microorganism which have grown upon the surface of the agar are then placed in a liquid solution and applied upon a second agar culture medium. Dry paper discs, each of which has been impregnated with a certain quantity of a specific antibiotic, are gently pressed upon the surface of the inoculated agar

and the isolate is then incubated for six to eighteen hours in contact with the discs.

During incubation, the antibiotics disseminate outward, forming circular zones around each of the paper discs. In the zones around the discs which were impregnated with a particular antibiotic to which the infecting microorganism is sensitive, no new culture of the microorganism isolate will grow, leaving a clear circle on the agar medium; in the zones around discs which were impregnated with an antibiotic to which the microorganism is resistant, the isolate will grow, leaving little or no clear area. From the presence and size of the clear zones of inhibition around the various discs, the microbiologist is able to advise the physician which of the antibiotics have demonstrated the greatest effectiveness against the infecting mircoorganism.

The entire process usually takes approximately 24 to 36 hours. In many situations the test is modified to the extent that the infecting microorganism is not first isolated; the original specimen from the patient is incubated on the agar medium while in contact with the antibiotic-impregnated discs. In such cases, usable results may be obtained in as little as eight hours.

In September 1960, after notice (25 Fed. Reg. 3084) and an opportunity for public participation, the Commissioner of Food and Drugs, under authority delegated by the Secretary of Health, Education, and Welfare, promulgated regulations requiring preclearance and batch certification of antibiotic sensitivity discs and of dry powders of antibiotics used for sensitivity testing in the diagnosis or treatment of disease (25 Fed. Reg. 9369). The order recited

that sensitivity discs initially had been exempted from certification requirements, but that, following "numerous complaints by the medical profession, hospitals, and laboratory technicians, the Food and Drug Administration made an extensive survey of the conditions surrounding the production and marketing" of discs and found them unreliable in their statements of potency with resultant impairment of their safety and efficacy (25 Fed. Reg. 9370). It was therefore deemed "vital for the protection of the public health" (*ibid.*) to adopt regulations requiring batch certification of antibiotic sensitivity discs.

Six manufacturers of antibiotic sensitivity discs and powders, including Difco Laboratories, the claimant herein, filed objections to the announced regulations prior to their effective date, but the Commissioner found the objections insufficient to require a hearing (26 Fed. Reg. 2596–2597). No judicial review of the promulgating order, as authorized by 21 U.S.C. 357(f) and 371(f), was sought by the manufacturers. The regulations became effective on March 28, 1961, and are published at 21 C.F.R. 147.

2. THIS LITIGATION

This case arose on May 25, 1962, as an *in rem* seizure proceeding against an interstate shipment of a number of cases of antibiotic sensitivity discs bearing the trade name "Bacto-Unidisk." The libel alleged that the Bacto-Unidisk (1) was a "drug" within the meaning of the Act, (2) was composed of specific antibiotic drugs, and (3) was neither certified nor exempted from certification, as required by Section

507 of the Act and the regulations issued thereunder (App. 5–6). Difco Laboratories, the manufacturer of the discs, appeared as claimant and admitted the allegations, except that it denied that the articles were "drugs," and thus that they were subject to the batch certification requirements under the statute (App. 7, 28–29; see App. 8–20). When the case came to trial in May 1965,[3] the only substantive question was whether the articles were "drugs," within the meaning of Section 201(g) of the Act, *supra*.[4] This issue arises because Section 507(a) of the Act, *supra*, defines "antibiotic drug" as "any drug * * *" and thus depends for its applicability on the Act's general definition of "drug" in Section 201(g).

The Bacto-Unidisk is a flat ring of three-sixteenths inch wide paper with an overall diameter of three and five-sixteenths inches. Extending inward from the ring are eight evenly-spaced protrusions each about three-eighths of an inch long. Seven of the protrusions terminate in one-quarter inch diameter circles; one terminates in a one-quarter inch square. Each of the one-quarter inch circles is impregnated with a different antibiotic, the name of which is printed on the outer ring at the base of the protrusion. The square is impregnated with a sulfonamide (sulfadiazine), a chemical which is used for therapeutic purposes but which is

[3] Cross motions for summary judgment were denied on April 6, 1965 (App. 29–31).

[4] The government contended in the courts below that the claimant was barred from raising this issue by its failure to seek judicial review of the order promulgating the regulation, but that issue was not raised in the petition for certiorari and the government does not in this Court challenge the claimant's standing to raise the statutory issue in this litigation.

not an antibiotic. The general appearance is that of a small paper wheel having eight spokes, with the central section (the hub and most of each spoke) punched out (Libelant's Exhibit 1; App. 34–35, 180–185).

The labeling enclosed with each carton of Bacto-Unidisks states that the disks contain standardized amounts of eight therapeutic agents, that they are "especially valuable in selecting the drug effective against chronic or persistent infections refractory to primary therapy", and that they are "recommended as a rapid, practical, clinically accurate and inexpensive means of determining the relative sensitivity of microorganisms to these therapeutic agents" (Libelant's Exhibit 1; App. 34–35, 180–185).

In use, the Bacto-Unidisk is employed in the same manner as other antibiotic sensitivity discs, following the general procedure described above (App. 8–20, 39, 42–43, 45–47, 183–185). The attachment of the individual discs to a common paper ring is designed only as a matter of convenience. It is undisputed on this record that the results of sensitivity testing guide the physician in his selection of a treatment agent, and help him rule out agents that are not effective or which are less effective against his particular patient's infection (App. 43, 47, 48, 51, 54, 60–61, 64–67, 69, 75, 77, 79, 104, 120, 122, 124, 127, 131, 136, 142–143).

Three expert witnesses, called by the government, Dr. Joseph Paul Truant, Chief Bacteriologist, Henry Ford Hospital, Detroit (App. 35, 82), Dr. Charles K. Wolfe, an internist specializing in infectious diseases

at the University of Illinois Medical School (App. 62), and Dr. Albert Martin Lerner, Chief of Infectious Diseases, Detroit Receiving Hospital and Associate Professor of Medicine, Pathology and Microbiology at Wayne State University School of Medicine (App. 134), testified that the Bacto-Unidisk was used as a guide in the treatment, cure, and prevention of disease (App. 47–48, 64, 67, 69, 75, 136, 142–143). Dr. Lerner said: "It is impossible to deal with a sick patient with an infection without dealing and grappling with disks and the results of these disks" (App. 136).

Claimant's expert medical witness, Dr. Chester S. Keefer, Professor of Medicine Emeritus, Boston University School of Medicine, a leader in the early development of antibiotic therapy, classified the disc as a laboratory agent (App. 107, 116). He took the view that medical diagnosis is an art in which the disc plays only a part, and that "without regard to any statutory terms or definitions," a drug "in the medical sense is a chemical or combination of chemicals that is used for the treatment of patients" or for "relief of symptoms" by local application, orally, or by injection (App. 123). He said that he did not know of any substance, from a medical standpoint, that would be classified as a drug which would not be used in that manner (App. 123). Thus, he concluded that the Bacto-Unidisk is not a drug in the medical sense, as he understood the term to be used. Nonetheless, Dr. Keefer testified that sensitivity discs are used in the course of treating patients with complicated infections who are not responding to a

broad spectrum antibiotic, and that, as a result of the disc tests, the treatment is frequently changed to another antibiotic (App. 123–124).[5]

In its memorandum opinion (App. 186–191) the district court held that even though a "literal reading" of Section 201(g)(2) "clearly has application to the article libeled herein" (App. 190), and "despite the fact that drugs are contained in the article," the Bacto-Unidisk does not come within the purview of the definition of "drug" for the reason that "no part of this article is administered to man or other animals, either internally or externally, and that its sole function is to provide medical doctors with information for use by them as guidelines" (App. 190–191). The court suggested, without deciding, that the discs would more appropriately be classified as "devices" under Section 201(h) of the Act, *supra* (App. 190).

The court of appeals affirmed, stating that the sole function of the discs is to furnish doctors with information which enables them to treat diseases previously diagnosed; that the discs have nothing to do with diagnosis or prevention of disease; and that, although the discs aid physicians in the determination of what antibiotic to use for the cure, mitigation or treatment of disease, Congress did not intend to apply the statutory phrase "intended for use in the * * * cure, mitigation, [or] treatment" in such an indirect manner (App. 199–200).

[5] The claimant's other witnesses established that antibiotic discs are not listed in the United States Pharmacopoeia or the National Formulary, and thus do not come within that portion of the definition of "drug" in Section 201(g)(1)(A).

SUMMARY OF ARGUMENT

Because of the peculiar scientific properties of antibiotic drugs, Section 507 of the Federal Food, Drug, and Cosmetic Act, *supra*, requires the batch testing of such drugs in order adequately to insure their safety and efficacy of use. Under authority delegated by that provision, the Secretary of Health, Education, and Welfare has determined, in a rule-making proceeding, that this batch-testing requirement applies to antibiotic sensitivity testing discs, which are impregnated with various antibiotic drugs and which are used to select the antibiotic most appropriate for treatment of a particular patient. This administrative determination serves the purpose of Section 507 by providing needed assurance that patients will get the therapeutic benefit intended when physicians prescribe antibiotic drugs.

The Secretary correctly interpreted the Act as authorizing the application of the batch-testing requirement to antibiotic discs. That interpretation is consistent with the language and legislative history of the Act and is in furtherance of the statutory purpose. This important public health legislation is properly interpreted functionally, so as to afford the public the statutory protections that are scientifically pertinent to the characteristics of the particular article at issue and to the medical use for which it is intended. The contrary interpretation by the courts below—which turns on usage of the word "drug" outside the statute, without regard to the statutory definition or statutory purpose—erroneously deprived

the public of the only statutory protection which is adequate to assure that antibiotic sensitivity discs will be safe and efficacious in use.

ARGUMENT

I

BATCH TESTING OF ANTIBIOTIC DISCS ACCORDS WITH THE PURPOSE OF CONGRESS, EXPRESSED IN SECTION 507 OF THE ACT, TO ASSURE THAT ANTIBIOTIC DRUGS USED IN THE TREATMENT OF DISEASE HAVE THE QUALITIES NECESSARY "TO ADEQUATELY INSURE SAFETY AND EFFICACY OF USE"

A. A PRINCIPAL PURPOSE OF SECTION 507 IS TO INSURE EFFICACY OF USE OF ANTIBIOTIC DRUGS

Section 507 of the Federal Food, Drug, and Cosmetic Act, *supra*, gives the Secretary of Health, Education, and Welfare the duty to provide by regulation "for the certification of batches" of antibiotic drugs to assure that they have such characteristics of strength, quality, and purity as are necessary "to adequately insure safety and efficacy of use."

As set forth in the statement, treatment of disease by antibiotic therapy has become increasingly important in recent years. One leading work on the subject[*] has said,

> The medical, public health, and economic aspects of antibiotics are difficult to overestimate, and the years elapsing since their introduction into therapy have witnessed dramatic reductions in the incidence of, and morbidity and mortality due

[*] Goodman & Gilman, *The Pharmacological Basis of Therapeutics*, 3d Ed. 1965, p. 1172.

to, a number of infectious diseases heretofore unresponsive to chemotherapy.

Because of the biological process by which antibiotic drugs are produced, variations in the products may easily occur and are difficult to detect. As a result antibiotic drug certification began in September 1943, when penicillin first became available as an anti-infective agent for use by the Armed Forces. (App. 114–115.) In 1945, when the wartime controls were relaxed, Congress first enacted Section 507 as an amendment to the Federal Food, Drug, and Cosmetic Act to impose this type of regulatory control. P.L. 79–139, 59 Stat. 463. While this provision initially applied only to penicillin, as new antibiotics having similar characteristics (see *supra*, p. 6) came into use, the requirement was extended: to streptomycin in 1947,[7] to aureomycin (chlortetracycline), chloramphenicol and bacitracin in 1949,[8] and to all other antibiotics for human use in 1962.[9]

Testifying in support of the 1962 Amendments to expand the certification program, the then Secretary of Health, Education, and Welfare, Mr. Ribicoff, said:

> These antibiotic drugs are the drugs of first choice in treating life-threatening infectious conditions. They affect a larger part of the population than any other drug used in similar conditions. Since they are employed in conditions where even minor delays in effective treatment may result in death, it is essential

[7] P.L. 16, 61 Stat. 11.
[8] P.L. 164, 63 Stat. 409.
[9] P.L. 87–781, 76 Stat. 785–787.

> that they be fully potent, absolutely safe, and properly labeled. It would be in the public interest and in the interest of good medical practice to require certification of all antibiotics, as provided in S. 1552.

Hearings before the Subcommittee on Antitrust and Monopoly, Committee on the Judiciary, United States Senate, 87th Cong., 1st Sess., September 13, 1961, p. 2590.

Certification requires that the sponsor of an antibiotic drug develop and present to the Secretary of Health, Education, and Welfare scientific data derived from preclinical and clinical investigations to establish the conditions of its safe and effective use. The Secretary then promulgates regulations, based upon the scientific data, establishing such standards of identity, strength, quality, and purity as are necessary adequately to insure safety and efficacy of the antibiotic for its intended use. Thereafter the sponsor submits to the government samples from each production batch of the antibiotic. These are examined and tested in government laboratories for compliance with the standards and with packaging, labeling, and advertising requirements. 21 CFR 146.2–146.4, 146.10, 147. In short, certification is a system of preclearance involving advance approval of the drug and its packaging, promotion, and labeling to assure safety and effectiveness in use.

The requirement for safety and "efficacy of use" means that antibiotic drugs are not, and cannot properly be, tested in and of themselves, separate and apart from the form in which they are used. If an anti-

biotic is used in a tablet or hypodermic dose, it is necessary to test the tablet or the liquid for assurance that it has its declared potency and will dissolve properly or be transmitted to the patient's bloodstream to treat his infection. In other words, batch-testing is not a theoretical, academic exercise; it is a method of assuring that, when the physician prescribes a particular antibiotic, the patient gets the treatment which the physician intended.

B. BATCH TESTING OF ANTIBIOTIC DISCS IS IN ACCORD WITH THE PURPOSE OF THE ANTIBIOTIC AMENDMENTS

Batch testing of antibiotic discs serves the purpose of the antibiotic drug amendments to protect the public health by ensuring that the patient will get the therapeutic benefit intended when a physician prescribes a particular antibiotic drug.

1. The rational use of antibiotics depends upon laboratory testing of the infecting organism to determine which drug or drugs may be effective against that organism. Goodman and Gilman, in their book, *The Pharmacological Basis of Therapeutics* (3d ed. 1965) state, at page 1174:

> The sensitivities of bacteria to various antimicrobial agents are usually determined by microbiological methods. The most accurate technic for use in the routine diagnostic laboratory involves inoculation of the organism being tested into a liquid culture medium in test tubes containing serial dilutions of the drug. After a suitable period of incubation, the lowest concentration of antibiotic inhibiting growth of the bacteria is expressed as the "sen-

sitivity". A more rapid method involves the use of commercially available filter-paper discs infiltrated with specific quantities of the drugs. These are placed on the surface of agar plates over which a culture of the organism being examined has first been streaked. Although this is a relatively crude procedure, the accuracy of which may be influenced by pH, size of inoculum, thickness of the agar medium, temperature of incubation, and the accuracy of the stated quantity of drug present in the paper disc, it is of practical clinical importance in indicating which antibiotic to employ and the general level of dose required to produce a therapeutic effect.

Antibiotic sensitivity discs and sensitivity testing procedures were developed commercially in 1949 or 1950 (App. 126) to provide such a rapid screening test. In the beginning, only three antibiotic drugs were involved. As new antibiotics were introduced into clinical practice, new discs were developed to facilitate the safe and effective use of these new therapeutic agents. Today, approximately 82 percent of the hospitals and clinical laboratories in the United States conduct senstivity tests prior to the initiation of antibiotic therapy,[10] and almost all antibiotic sensitivity

[10] Isenberg, *A Comparison of Nationwide Microbial Susceptibility Testing Using Standardized Discs*, 1 Health Laboratory Science 185, 186 (1964).

Such testing not only serves to assure that the particular patient will receive an appropriate and effective antibiotic, it also helps to prevent the selection of unneeded special-purpose antibiotics prone to engender the development of resistant strains of infecting organisms. This has led the Expert Committee on

testing is carried out by the use of commercially prepared antibiotic impregnated discs.[11] Extensive bacteriological investigations have been conducted to validate the disc method of sensitivity testing, and it is accepted today that the results yielded by properly prepared discs, properly interpreted, are reliable guides to antibiotic therapy.[12]

2. Critical to the reliability, safety and effectiveness of the antibiotic discs are assurance of identity, strength, quality and purity of the antibiotic drugs used to impregnate the disc; proper packaging to prevent deviations from those standards before use;

Antibiotics of the World Health Organization to conclude that sensitivity testing is "essential * * * for preserving the efficacy of this important group of therapeutic substances" by limiting their use to the special circumstances in which they are uniquely effective. Second Report of the Expert Committee on Antibiotics, *Standardization of Methods for Conducting Microbic Sensitivity Tests*, World Health Organization Technical Report Series No. 210, p. 3 (1961).

[11] Rose and Berky, *A Quality Control System for Disk Antibiotic Testing*, 48 American Journal of Clinical Pathology 200 (1967).

[12] See, generally, Truant, Bolin, and Mullins, *Evaluation of Susceptibility Testing Procedures with Single and Multiple Antibiotic Discs*, Antimicrobial Agents and Chemotherapy, 384, 393–394 (1964); Bauer, Kirby, Sherris, and Turck, *Antibiotic Susceptibility Testing by a Standardized Single Disk Method*, 45 American Journal of Clinical Pathology 493, 496 (1966); Rose and Berky, *A Quality Control System for Disk Antibiotic Testing*, 48 American Journal of Clinical Pathology 200, 212–213 (1967).

and proper labeling to provide the physician information as to how long the disc may be expected to be reliable (an expiration date) and how the results of disc testing are to be interpreted in applying them to the clinical situation.[13]

Excessive potency, for example, may falsely indicate that the patient's infection is susceptible to treatment with that particular antibiotic.[14] Failure to package the disc properly with a desiccant to prevent moisture uptake may substantially affect the diffusion of the antibiotic drugs from the disc into the bacterial growth medium.[15] Labeling may fail to provide proper information for interpreting the results of the disc test. Just as a patient's life may be endangered by an improper tablet, a patient's life may well be jeopardized by a disc which contains, *e.g.*, an excess in potency with too rapid diffusion, giving a false reading

[13] See, *e.g.*, Second Report of the Expert Committee on Antibiotics, *Standardization of Methods for Conducting Microbic Sensitivity Tests*, World Health Organization Technical Report Series No. 210, pp. 12–13 (1961); Truant, Bolin, and Mullins, *Evaluation of Susceptibility Testing Procedures with Single and Multiple Antibiotic Discs*, Antimicrobial Agents and Chemotherapy 384 (1964); Bauer, Kirby, Sherris, and Turck, *Antibiotic Susceptibility Testing by a Standardized Single Disk Method*, 45 American Journal of Clinical Pathology 493, 496 (1966).

[14] See, *e.g.*, Rose and Berky, *A Quality Control System for Disk Antibiotic Testing*, 48 American Journal of Clinical Pathology 200, 204 (1967); Murayama, *Fundamental Study on the Disc Method of Antibiotic Sensitivity Test*, 12 Journal of Antibiotics, Ser. A, 263 (1959).

[15] See Ostrander and Griffith, *An Evaluation of Different Types of Paper Concerning Their Suitability for Sensitivity Discs*, Antibiotics Annual 1958–1959, p. 813, at p. 817; Griffith and Mullins, *Drug Resistance as Influenced by Inactivated Sensitivity Discs*, 16 Applied Microbiology 656 (1968).

of sensitivity to that particular antibiotic. False readings result in misinformation to the physician, with the result that the patient is not treated properly.[16]

Indeed, the labeling for most of the antibiotics listed in 21 C.F.R. 145.3—and thus available for marketing—contains directions that the drug is to be used against known sensitive organisms, or after antibiotic sensitivity testing of the patient's organisms or bacteriologic tests of the sort provided by the sensitivity units. See the *Physicians' Desk Reference to Pharmaceutical Specialties and Biologicals* (1968). The directions for Unipen (p. 1244), for example, state, "Therapy with this product, like that with all other potent antimicrobials, should always be accompanied by appropriate bacteriologic culture studies." The revised monograph for Lincocin (Supplement B, p. B27) tells the physician to "[d]o in vitro culture and susceptibility studies in conjunction with Lincocin therapy." And the revised labeling requirements for chloramphenicol, one of the antibiotics in the Bacto-Unidisk, warn that because of its dangerous and sometimes fatal side effects, "[s]ensitivity testing is essential to determine its indicated use."[17]

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[16] The result of such misinformation can be to "deny the patient the use of a life-saving drug" or to give the patient "a drug that would have little or no therapeutic value to him," thus presenting a "serious health hazard." Greenberg and Fitzpatrick, *On the Control of Antibiotic Discs in Canada*, 79 Canadian Medical Association Journal 383 (1958).

[17] The prescribing directions for this antibiotic were revised in May 1968 by a notice to all physicians in the United States, subsequently published at 33 Fed. Reg. 15566 (October 18, 1968), which stated: "Chloramphenicol is an antibiotic that is clinically useful for, *and should be reserved for*, serious infec-

The reliability of antibiotic sensitivity testing affects both the safety and the effectiveness of the patient's treatment. This is true whether the disc is used before or concurrent with the initiation of therapy. The record is clear that the results of the tests performed with the disc are used by the physician as a guide to his selection of the most appropriate antibiotic for treatment of his patient's infection (*e.g.*, App. 43, 47, 51, 60, 64–65, 75, 79, 104, 120, 136, 142–143). In fact, as a result of the test with the disc, the antibiotic being given the patient may be switched at a critical point when he is not responding to the primary therapy (App. 61, 123–124, 127, 131, 142–143).

Proper selection of a safe and effective drug in treating infections, particularly when the infection is refractory and life-threatening, thus depends in substantial measure upon the reliability of antibiotic discs, such as the Bacto-Unidisk, to aid the physician in promptly identifying the drug that is best for ad-

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tions caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see 'Indications' section)." (Emphasis in original.) Under "INDICATIONS," the physician is advised that while chloramphenicol "MAY BE CHOSEN TO INITIATE ANTIBIOTIC THERAPY ON THE CLINICAL IMPRESSION THAT ONE OF THE CONDITIONS * * * [LISTED] IS BELIEVED TO BE PRESENT; IN VITRO SENSITIVITY TESTS SHOULD BE PERFORMED CONCURRENTLY SO THAT THE DRUG MAY BE DISCONTINUED AS SOON AS POSSIBLE IF LESS POTENTIALLY DANGEROUS AGENTS ARE INDICATED BY SUCH TESTS." (Emphasis in original.)

ministration to his critically ill patient. As one of the witnesses stated (App. 67):

> I think the antibiotic choice is the thing I particularly used it for, and the reason I use antibiotics is to effect a cure.

In short, the Bacto-Unidisk is intended to be, and is, used in the course of treatment of disease.

3. Batch testing of discs is as important to assuring the safety and efficacy of use of antibiotic drugs as batch testing of tablets, hypodermic dosages, etc. As discussed above, all the qualities which led Congress to require batch testing—the importance of the drug, the variations resulting from biological processes, the need to have the drug in a proper medium—apply as fully to the antibiotics in a disc as to antibiotics in a tablet.

Experience has shown that batch certification is the only practical means of providing assurance of disc reliability. Since the initiation of certification requirements, commentators have acclaimed the step and noted that the certified discs have proven reliable in clinical use.[18] Prior to the promulgation of the certification requirements, however, the Food and Drug Administration's survey which preceded its action in requiring certification of antibiotic discs established that unreliable discs were then being marketed.

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[18] *E.g.*, Griffith and Mullins, *Drug Resistance as Influenced by Inactivated Sensitivity Discs*, 16 Applied Microbiology 656, 658 (1968); Truant, Bolin, and Mullins, *Evaluation of Susceptibility Testing Procedures with Single and Multiple Antibiotic Discs*, Antimicrobial Agents and Chemotherapy 384 (1964).

25 Fed. Reg. 9370. A Canadian survey had shown that discs manufactured in the United States not only were unreliable, but that the assayed content of antibiotics "rarely correspond[ed] to the labeled potency."[19] The commercially available discs were found to vary from 2 percent to 400 percent of their labeled potency, and discs were occasionally found to contain degradation products and traces of antibiotics other than the ones specified.[20]

The Pharmaceutical Manufacturers Association was aware of, and concerned about, the problems.[21] Papers from the academic community noted the serious difficulties of obtaining meaningful information from the routinely used disc tests.[22] Indeed, the problem of disc reliability and disc standardization was of world-wide concern.[23] The Pasteur Institute exercised control over

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[19] Branch, Starkey, Power, and Greenberg, *Problems of Standardization of Manufactured Dry Penicillin Sensitivity Discs*, Antibiotics Annual, 1956–1957, p. 898, at p. 904.

[20] Greenberg, Fitzpatrick and Branch, *The Status of the Antibiotic Disc in Canada*, 76 Canadian Medical Association Journal 194 (1957); Greenberg and Fitzpatrick, *On the Control of Antibiotic Discs in Canada*, 79 Canadian Medical Association Journal 383 (1958).

[21] Gerwe, *Problems Encountered in the Manufacture of Commercial Sensitivity Discs*, Antimicrobial Agents Annual 1960, p. 465. Dr. Gerwe noted that the prescribing physician "has every right to demand that the results obtained be reliable. We are dealing with human lives and we should take any step necessary to better the precision of this test" (*id* at 466).

[22] *E.g.* Branch, Starkey, Power, and Greenberg, *Problems of Standardization of Manufactured Dry Penicillin Sensitivity Discs*, Antibiotics Annual 1956–1957, p. 898.

[23] Branch, Starkey, and Power, *The International Situation with Regard to the Use of Discs for Antibiotic Sensitivity Tests*, Antibiotics Annual, 1958–1959, p. 833.

antibiotic discs sold in France.[24] Canada began to require certification of antibiotic discs in 1958.[25] And in 1961, the World Health Organization recommended that "each government should ensure some system of control over the quality and particularly the antibiotic content of such commercially prepared discs."[26]

Expressions of similar concern about the standardization and reliability of antibiotic discs led to the administrative study which resulted in promulgation of the regulation requiring batch certification of antibiotic sensitivity discs (see Statement, *supra*, p. 9). That study resulted in an administrative determination, which was not challenged by judicial review of the rule-making proceeding, that results yielded by sensitivity tests with discs impregnated with an improper amount of an antibiotic drug, or with discs which did not properly diffuse their antibiotic drugs into the bacterial growth media, were posing a real danger of improper and ineffective therapy with the wrong drug at a critical stage of the patient's course of treatment.

Moreover, the government established at the trial of the present case that there is an important medical need for the certification of antibiotic discs because of the danger to patients of basing treatment upon results drawn from unreliable sensitivity units.

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[24] See Branch, Starkey, Power, and Greenberg, *supra*, at 904.

[25] Trade Information Letter No. 164, dated November 3, 1958, of the Department of National Health and Welfare, Canada.

[26] Second Report of the Expert Committee on Antibiotics, *Standardization of Methods for Conducting Microbic Sensitivity Tests*, World Health Organization Technical Report Series No. 210, p. 13 (1961).

Dr. Truant testified: that "false readings" would be obtained from improperly prepared discs and that the physician consequently "would not treat the patient properly" (App. 83); that poor standardization would result in production of discs "of poor quality, which would give misinformation" to the laboratory and the clinician (App. 84); and that while he could not put his finger on a specific example in which a physician had been misled to the detriment of a patient, he could "recall that there were a number of instances brought to my attention by individuals in the infectious disease department." (App. 93).

Dr. Lerner was asked on cross-examination whether he thought "the public health was involved" in disc reliability. He replied that he did (App. 141). While he personally had not seen a case of patient harm from a faulty disc, he had on some occasions discarded disc data as unreliable because it was inconsistent with other information concerning the patient's condition (App. 141). Dr. Lerner was asked on direct examination about the importance of disc standardization and reliability. He answered, "I feel that it is vital" (App. 139). Hospital laboratories, he said, were unable to test discs for performance, and thus had to rely upon the label representations as to their composition and performance (App. 139–140).

The physician on the front line of clinical practice simply has to accept the discs as having their professed identity, strength, and quality, and as suitable to yield the results claimed in their labeling. The physician does not have the time, the knowledge, the facilities, or the experimental patients needed to test the discs

for potency and performance before using them to determine the sensitivity of his patient's infection to the array of antibiotic drugs packaged on the disc (App. 89, 139–140).

The physician is told repeatedly (see *supra*, p. 22) to do sensitivity testing before or while treating with an antibiotic to assure that the patient's infection is sensitive to the antibiotic he has chosen. Both the physician and the patient can be misled and harmed, even though there is assurance that the capsule, pill or injection is potent and pure, if the sensitivity unit does not reliably give the same sort of assurance that the antibiotic chosen is the proper one. Batch testing of antibiotic discs serves the function for which batch testing of antibiotic drugs was designed—to assure that antibiotic drugs administered to patients are safe and effective in use.

II

THE SECRETARY PROPERLY INTERPRETED THE ACT AS AUTHORIZING THE APPLICATION OF THE BATCH TESTING REQUIREMENT TO ANTIBIOTIC DISCS

1. The courts below did not, essentially, dispute either the need or the desirability of batch testing of antibiotic discs. Nor did they find that such testing would be incompatible with the purposes of Section 507 of the Act. Their holding is based on the view that, whether scientifically needed or not, batch testing of the discs cannot be required by regulation because the Act authorizes the Secretary to impose

such requirement only for "drugs" and, in their view, the antibiotic discs are not "drugs."

Despite the contrary suggestion by the court of appeals (App. 199–200), it is, we submit, clear, as the district court acknowledged (App. 190), that the discs fall within the literal definition of "drug" in Section 201(g) as "articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease." While the disc does not itself make a diagnosis or treat the patient, it plays an essential role in the selection of an appropriate remedy for serious disease. As a result of information as to the inhibiting action of the particular drug on the patient's particular infectious microorganisms, the infection is diagnosed as one sensitive to a particular antibiotic, and the patient is treated with that particular drug. This is certainly a use in the diagnosis and treatment of disease.

The more substantial question in this case is how to draw the line between "drug" as defined in Section 201(g) and "device" which is defined ~~in almost~~ identical terms in Section 201(h) as "instruments, apparatus, and contrivances * * * intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease * * *." The answer to that question, we think, was given by this Court, in dealing with a similar statutory problem, in *Securities and Exchange Commission* v. *Ralston Purina Co.*, 346 U.S. 119, 124–125. There, in interpreting the statutory exemption from registration for a private offering of stock, the Court said that the "natural way to interpret the private offering exemption is in light of the statutory

purpose." Finding that it was the congressional intent to exempt transactions as to which there was no practical need for the statute's application, the Court ruled that the interpretation of the exemption "should turn on whether the particular class of persons affected needs the protection of the Act." Applying this standard, the Court held, without any reference to usage of the term "public offering" outside the statute, that the company's offering of treasury stock to its "key employees" was a "public offering" subject to the provisions of the Securities Act because the employees had not been "shown to be able to fend for themselves * * *" (*ibid.*).

There is even more reason in the present case than in *Ralston Purina* to be guided by the policy of the statute, and to eschew reference to usage outside the statute,[27] in construing the statutory term at issue. The term "public offering" was nowhere defined in the Securities Act (see 346 U.S. at 122). Here the word "drug" is a statutory term of art, defined in Section 201(g) "[f]or the purposes of this Act", and the discs do, as noted above, fall within the literal terms of the statutory definition.

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[27] The classification of discs as drugs is not as contrary to common medical usage as the district court seemed to believe. "Drug" is defined in Dorland's *Illustrated Medical Dictionary*, 24th Ed., p. 449 (1965), as: "Any chemical compound or any non-infectious biological substance, not used for its mechanical properties, *which may be* administered to or *used* on or *for patients*, either human or animal, *as an aid in the diagnosis, treatment* or prevention of disease or other abnormal condition, for the relief of pain or suffering, or to control, or improve any physiological or pathological condition." (Emphasis added.) This "medical" definition is not dissimilar to that in Section 201(g).

Since the literal terms of the definitions of drug and device overlap, the "natural way" to draw the line, as *Ralston-Purina* explained, "is in light of the statutory purpose." The qualities of antibiotics which led Congress to impose the requirement of batch testing are the same whether the drug is used for a pill, for a hypodermic injection, or as a test to determine what pill or injection to administer. The need for assurance as to quality and potency is essentially the same whether the antibiotic is used on a disc or in a pill or injection. Not only are physicians equally unable to make tests to determine potency, etc., whether the antibiotic is used in a pill or injection or on the disc, but patients—the class of persons that the Act is designed to protect—will derive little benefit from the Act's purpose of assuring that the antibiotic drugs administered to them are safe and properly potent if unreliability of the antibiotic sensitivity discs results in administration of the wrong drug or the wrong amount of drug to them.

In short, the whole purpose of batch testing of antibiotics for safety and efficacy of use applies to the discs of antibiotics. It was, therefore, entirely reasonable for the Secretary to conclude that the discs are drugs under Section 201(g), subject to the batch testing requirements of Section 507.[28]

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[28] Sensitivity discs and sensitivity tablets are classified as "drugs" under Canadian law and regulations. Their Food and Drugs Act defines "drug" and "device" in language similar to that involved in this case. Food and Drugs Act, 1953, 1-2 Eliz. II, c. 38, § 2(e) and (f) (Can.). Pursuant to authority granted by that Act (Section 24), the Governor General in Council, on the recommendation of the Minister of National Health and

2. This interpretation of the statute accords with the settled principle that the Federal Food, Drug, and Cosmetic Act is properly given a broad construction in accord with its purpose to protect the public health. *United States* v. *Sullivan*, 332 U.S. 689. This Court's decisions in *United States* v. *Coca Cola Co.*, 241 U.S. 265, and *62 Cases of Jam* v. *United States*, 340 U.S. 593, 596, have emphasized that it is within "the right and the wisdom" of Congress to provide its own glossary of terms and definitions in the Federal Food, Drug, and Cosmetic Act, and that the judicial function is to apply what the Congress has written. The fundamental error of the courts below lies in their application of what they believed to be the common medical usage of the term "drug" to a complex, technical, regulatory scheme designed for protection of the public health, without regard to either the statutory definition of the term or the purpose of the statute.

The more reasonable approach, in accord with the principles laid down by this Court, is that taken by the Court of Appeals for the Second Circuit in *AMP, Inc.* v. *Gardner*, 389 F. 2d 825, 830 certiorari denied *sub. nom. AMP, Inc.* v. *Cohen*, No. 86, this Term (Oct. 14, 1968), which rejected the idea that this important public law was "restricted to products commonly called "drugs'." Long before that, the Court of Appeals for the Fifth Circuit, interpreting the "drug" definition of the 1906 Food and Drugs Act, rejected as "entirely too narrow" a contention that spring water offered

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Welfare, issued regulations in 1958 which categorized antibiotic sensitivity discs as drugs and provided for their standardization. Food and Drug Regulations, C. 05.061–C. 05.067 (Can.).

for use in treating disease could not be regarded as a "drug" because dictionaries and pharmacopoeias did not so define the term. *Bradley* v. *United States*, 264 Fed. 79, 81. The Act is properly applied functionally to afford the public the protections of the statute that are scientifically pertinent to the characeristics of the particular article at issue and to the medical use for which it is intended. Since batch testing of discs clearly serves the purposes of protecting the public and since the discs do fall within the literal language and evident purpose of Section 507, the Secretary properly directed that they be subject to batch testing.

3. There is nothing in the legislative development of the definition of "drug" that discloses a congressional intent to preclude the application of the batch-testing requirement to articles like antibiotic discs, which are literally within its terms.

The 1906 Food and Drugs Act defined "drug" to include "all medicines and preparations recognized in the United States Pharmacopoeia or National Formulary for internal or external use, and any substances or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals". 34 Stat. 768, 769. One of the significant improvements made by the Federal Food, Drug, and Cosmetic Act in 1938 was the expansion of the definition of "drug". The need for this was pointed out at the very first Senate hearing, Hearing before the Senate Committee on Commerce on S. 1944, 73d Cong., 2d Sess., by the Chief of the Food and Drug Administration. Dunn, *Federal Food, Drug, and Cosmetic Act* (1938), p. 1053. The

first Senate Committee Report, S. Rep. 493, 73d Cong., 2d Sess., on S. 2800, reflected the change. That bill defined "drug" to include "(1) all substances and preparations recognized in the United States Pharmacopoeia, Homoeopathic Pharmacopoeia of the United States or National Formulary or supplements thereto; and (2) all substances, preparations, and devices intended for use in the cure, mitigation, treatment, or prevention of disease in man or other animals; and (3) all substances and preparations, other than food, and all devices intended to affect the structure or any function of the body." S. 2800, Sec. 2(b), Dunn, *supra*, at 72.

The definition was revised in S. 5, 74th Cong., 1st Sess.; S. Rep. 361, 74th Cong., 1st Sess. (March 26, 1935), Dunn, *supra*, at 237, 239, to include substances, preparations and devices intended for diagnostic purposes. S. 5, Sec. 201(b), Dunn, *supra*, at 214. A controversy over this definition developed on the Senate floor, Senator Bennett Clark contending that it was not proper to classify devices as drugs, and that diagnostic devices were so broadly defined as to make even a bathroom scale a drug. Dunn, *supra*, at 286–296. Senator Copeland, the Senate sponsor, proposed an amendment to add a definition of "device", parallel to that for "drug", but the drug definition was unchanged except for that revision. Dunn, *supra*, at 495–496.

Later explanations of the "drug" definition were brief, but they made it clear that Congress knew the definition was a broad one. For example, S. Rep. 2139, 75th Cong., 3d Sess., said: "The definition of drug is

expanded to include articles used in the diagnosis of disease, and articles other than food intended to affect the structure or any function of the body of man or other animals. These expansions are needed to give jurisdiction over a great number of drugs which are not amenable to control under the present law." Dunn, *supra,* at 817.

This history negates the conclusion of the district court that the definition of drug in Section 201(g) was intended by Congress to be restricted to "articles administered to man or other animals, either internally or externally." The term drug was intended to be as broad as necessary to accomplish the general purpose of the Act to protect the health of the nation.

Nothing in the legislative history precludes a reasonable interpretation of the term drug designed to accomplish the evident purpose of Section 507 to assure that any antibiotic used in the treatment of disease in man would be effective for its intended use. In Section 507, Congress required the certification of antibiotic drugs "as necessary to adequately insure safety and efficacy of use." "Efficacy," used here, carries its plain meaning. As explained by Secretary Ribicoff in 1962, in testifying before a House of Representatives committee considering the use of the term in the bill which was eventually enacted as Section 507 (Hearings Before the Committee on Interstate and Foreign Commerce, House of Representatives, 87th Cong., 2d Sess., p. 80):

"[E]fficacy" means that it is effective to do the job that it is represented to do. If it is represented to effect a cure, it will effect such a cure. If it is represented to clear up a condition, it will clear up a condition.

Many drugs on the market might be safe but absolutely useless to effect what they are represented to accomplish.

If antibiotics administered to patients are to be effective, the antibiotic sensitivity discs must also be effective. If, as Congress has determined, batch testing is necessary to insure the efficacy of antibiotic drugs in use, batch testing is equally necessary to insure the efficacy of antibiotic discs. The legislative history supports the view that the term "drug" can and should properly be construed to accomplish that beneficial purpose.

CONCLUSION

For the foregoing reasons, the judgment of the court of appeals should be reversed and the case should be remanded for the entry of an appropriate decree of condemnation.

Respectfully submitted.

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UNITED STATES OF AMERICA,
Petitioner,

v.

AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * *

On Writ of Certiorari to the United States Court of Appeals for the Sixth Circuit

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BRIEF FOR CLAIMANT DIFCO LABORATORIES, INC.

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1968

No. 343

UNITED STATES OF AMERICA,
Petitioner,

v.

AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * *

On Writ of Certiorari to the United States Court of Appeals for the Sixth Circuit

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BRIEF FOR CLAIMANT DIFCO LABORATORIES, INC.

QUESTION PRESENTED

Whether a sensitivity disk utilized as part of a laboratory testing procedure which yields information the physician may use as a guideline to the changing or selection of an antibiotic to treat patients who have not responded to initial therapy, is a "drug" within the meaning of Section 201(g)(1)(B) of the Federal Food, Drug, and Cosmetic Act and, if it is a "drug", whether it is subject to batch certification under Section 507 of the Act.

STATUTE INVOLVED.

The Federal Food, Drug, and Cosmetic Act, 52 Stat. 1040 (1938), as amended, 21 USC 301 et seq., provides in part:

Sec. 201 (21 USC 321)

(j) The term "official compendium" means the official United States Pharmacopeia . . . official National Formulary, or any supplement to any of them.

* * * *

(n) If an article is alleged to be misbranded because the labeling is misleading, then in determining whether the labeling is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling relates under the conditions of use prescribed in the labeling thereof or under such conditions of use as are customary or usual.

Sec. 301 (21 USC 331)

The following acts and the causing thereof are hereby prohibited:

(a) the introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.

* * * *

(d) the introduction or delivery for introduction into interstate commerce of any article in violation of section . . . 505.

* * * *

(f) The refusal to permit entry or inspection as authorized by section 704.

* * * *

(p) The failure to register as required by section 510.

* * * *

Sec. 303 (21 USC 333)

(a) Any person who violates any of the provisions of section 301 shall be guilty of a misdemeanor and shall on conviction thereof be subject to imprisonment for not more than one year, or a fine of not more than $1,000, or both such imprisonment and fine; but if the violation is committed after a conviction of such person under this section has become final such person shall be subject to imprisonment for not more than three years, or a fine of not more than $10,000, or both such imprisonment and fine * * *

(b) Not withstanding the provisions of subsection (a) of this section, in case of a violation of any of the provisions of section 301, with intent to defraud or mislead, the penalty shall (except in the case of an offense which is subject to the provisions of the proviso to subsection (a) relating to second or subsequent offenses) be imprisonment for not more than three years, or a fine of not more than $10,000, or both such imprisonment and fine.

* * * *

Sec. 403 (21 USC 343)

A food shall be deemed to be misbranded . . . (c) If it is an imitation of another food, unless its label bears . . . the word "imitation" and, immediately thereafter, the name of the food imitated.

* * * *

(g) If it purports to be or is represented as a food for which a definition and standard of identity has been prescribed by regulations as provided by section 401, unless

(1) it conforms to such definition and standard, and (2) its label bears the name of the food specified in the definition and standard, and, insofar as may be required by such regulations, the common names of optional ingredients (other than spices, flavoring, and coloring) present in such food.

* * * *

Sec. 501 (21 USC 351)

A drug or device shall be deemed to be adulterated-(a) . . . (2) . . . (B) if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess; or (3) if it is a drug and its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health; or (4) if (A) it is a drug which bears or contains, for purposes of coloring only, a color additive which is unsafe within the meaning of section 706(a), or (B) it is a color additive the intended use of which in or on drugs is for purposes of coloring only and is unsafe within the meaning of section 706(a).

(b) If it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standard set forth in such compendium . . .

(c) If it is not subject to the provisions of paragraph (b) of this section and its strength differs from, or its purity or quality falls below, that which it purports or is represented to possess.

Sec. 502 (21 USC 352)

A drug or device shall be deemed to be misbranded—

(a) If its labeling is false or misleading in any particular.

* * * * *

(f) Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users: *Provided*, That where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement.

(g) If it purports to be a drug the name of which is recognized in an official compendium, unless it is packaged and labeled as prescribed therein: *Provided*, That the method of packing may be modified with the consent of the Secretary.

* * * * *

(j) If it is dangerous to health when used in the dosage, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof.

* * * *

Sec. 505 (21 USC 355)

(a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Sec-

retary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug * * *

Sec. 507 (21 USC 357)

'(f) Any interested person may file with the Secretary a petition proposing the issuance, amendment, or repeal of any regulation contemplated by this section. The petition shall set forth the proposal in general terms and shall state reasonable grounds therefor. The Secretary shall give public notice of the proposal and an opportunity for all interested persons to present their views thereon, orally or in writing, and as soon as practicable thereafter shall make public his action upon such proposal. At any time prior to the thirtieth day after such action is made public any interested person may file objections to such action, specifying with particularity the changes desired, stating reasonable grounds therefor, and requesting a public hearing upon such objections. The Secretary shall thereupon, after due notice, hold such public hearing. As soon as practicable after completion of the hearing, the Secretary shall by order make public his action on such objections. The Secretary shall base his order only on substantial evidence of record at the hearing and shall set forth as part of the order detailed findings of fact on which the order is based. The order shall be subject to the provisions of section 701(f) and (g).

* * * *

Sec. 701 (21 USC 371)

* * * (f) (1) In a case of actual controversy as to the validity of any order under subsection (e), any person who will be adversely affected by such order if placed in effect may at any time prior to the ninetieth day after such order is issued file a petition with the Circuit Court of Appeals of the United States for the circuit wherein such person resides or has his principal place of business, for a judicial review of such order. A copy of the petition shall be forthwith transmitted by the clerk of the court to the Secretary or other officer designated by him for that purpose. The Secretary thereupon shall file in the court the record of the proceedings on which the Secretary based his order, as provided in section 2112 of title 28, United States Code.

* * * *

(f) (6) The remedies provided for in this subsection shall be in addition to and not in substitution for any other remedies provided by law.

* * * *

SUMMARY OF ARGUMENT

The antibiotic disk sensitivity test is used to obtain an indication of whether an infectious organism which has proved resistent to an antibiotic drug or drugs administered *before* the results of the test have been obtained, is sensitive *in vitro* to another drug or drugs. If the organism is sensitive *in vitro* to a particular antibiotic, that drug may be suitable for treatment of the patient suffering from the infection. Whether, if found sensitive *in vitro*, it would be administered to the patient, would depend upon many factors taken into consideration by the physician, other than the results of the test.

The physician always has a choice of more than one antibiotic both before and after the test is run. There

are many built-in protections which preclude the choice of the wrong antibiotic as the result of the use of a faulty disk in a sensitivity test. These are reviewed in Point I of the Argument and apparently were ignored or not understood at the time the Food and Drug Administration decided that disks should be made subject to certification. That proceeding did not involve the particular disk before the court and, in any event, no review of the decision by the Court of Appeals was available to any party (Point V).

The testimony and findings show that the disk is not used in "diagnosis" or "treatment" and is not a "drug" for that reason alone. Further, it is not a "drug" because it is not used in or on the body. The principal argument of the Government—that the disk should be classified as a drug to protect the public—would involve an unconstitutionally vague application of the statute (Point II).

The certification provisions of Section 507 of the statute would not be applicable to the disk, even if it were used in "diagnosis" or "treatment" of disease within the meaning of Section 201(g)(1)(B), and were therefore a "drug" under that section, because only antibiotic drugs administered or applied to patients were intended by Congress to be subject to certification.

ARGUMENT

Introduction

1. The statement of the Question Presented (Pet. Br. 2) is inaccurate and misleading.

Thus, to pose the question of whether sensitivity disks "containing various antibiotic drugs" are "antibiotic drugs" under the Act prejudges the very point at issue. The obvious and necessary implication is that the chemicals on the disks are drugs in some sense, presumably in

the common understanding of that term, i.e., that they are medicines (Webster's New International Dictionary). The implication is misleading. The chemicals are not available for use as drugs, not being in dosage form and being suitable only for use in laboratory testing procedures.

Moreover, the fact that Bacto-Unidisks contain chemicals commonly used as drugs, i.e., antibiotic substances and sulfadiazine, has nothing to do with the question of whether the disk itself is a drug since, as the court of appeals recognized, it is the "intended use" of an article which determines whether it falls within the definition of "drug", i.e., whether it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease (App. 201).[1] Thus, neither the disk itself nor the chemicals with which it is impregnated are drugs unless intended for such use.

The phrase in the Question Presented, "disks which physicians use to select the antibiotic most appropriate to treat a particular patient", being unqualified, conveys the idea that before an antibiotic is administered by the physician the disk indicates the proper drug to be used for the particular condition of the patient. This is not in accordance with the evidence. It is shown in the Argument that it is not the disk but the information derived from the entire testing procedure which may be used by the physician when he receives it—ordinarily some 24 to 36 hours or more after initial therapy has begun. Moreover, it is the laboratory worker who "uses" the disk and reports to the clinician.

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[1] As the court of appeals also noted (App. 201), even honey may be a "drug" under the Act if it is intended for use in the treatment of disease within the meaning of Sec. 201(g)(1)(B); but surely no rational person would suggest that its use in a laboratory testing procedure would constitute a use in the treatment of disease.

The Question Presented in the petition has been restated for the reasons set forth above.

2. The Government's statement of the case presages some of the dubious and unsupportable positions advanced in its argument.

It is the Government's contention that the public health need which Congress saw in 1947 for the certification of penicillin (and later for other antibiotic drugs) is translatable to a need for the certification of sensitivity disks used for laboratory testing, because they bear antibiotic substances and because certification is allegedly needed to assure the safety and efficacy of use of antibiotics administered to patients.[2] The argument will not stand examination. It is fully clear that the legislative record discussed in the brief was based on the need for certification of antibiotic drugs administered to or applied to patients. The record is entirely inconsistent with any other interpretation, as is demonstrated in Point III, *infra*. Sensitivity disks are not administered to or applied to patients in any way and the disks were not even in existence commercially when the certification provisions of the statute (Section 507) were enacted in 1945 (App. 126). The history recited in the brief is therefore irrelevant to the question of certification of the disks and lends no support to the Government's attempt to find a public health issue which it hopes will sway this court.

As we shall show, the effort to equate the need seen by Congress for the certification of dosage forms of antibiotic drugs with the alleged need for certification of sensitivity disks is not supported by any probative evidence adduced at the trial of this case in the District

[2] The notion that the disks should be controlled on the ground that control is necessary to assure safety and efficacy of use of other products, i.e., antibiotics administered to patients, is not relevant to Section 507. If disks are certifiable it is because of the nature and use of the disks, not because of the nature and use of other products.

Court. Nor is it supported by the extra-record publications cited, for the first time, in the Government's brief in this Court.[3]

I.

There is no Public Health Reason for the Certification of Antibiotic Sensitivity Disks

A. *Basic Considerations*

The brief for the United States pictures the Bacto-Unidisk (and other sensitivity disks) as dreadfully dangerous articles which need close government supervision in order to save the lives of patients. The difficulty is that (a) the principal basis for the attempted shock treatment is a series of publications *dehors* the record in the trial court with respect to which neither the authors nor any expert witness were subject to examination by claimant Difco Laboratories, Inc.[4] and (b) the ultimate conclusions drawn in the Government's brief from the publications in question are erroneous and unsound and show a basic lack of understanding of the function of sensitivity disks.

It is improper and grossly unfair to the claimant for the Government to go through a trial on the merits of the question of whether the Bacto-Unidisk is a drug without even attempting to support its case with the publications in question or with testimony of their authors, and then, for the first time in this court to ask the court to con-

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[3] *E.g.*, Greenberg and Fitzpatrick, *On the Control of Antibiotic Disks in Canada*, 79 Canadian Medical Association Journal 383 (1958) (Pet. Br. 22), state that faulty disks "present a serious health hazard", but offer no facts to support the assertion.

[4] With the exception of Dr. Truant (Ph. D.). He was the only author presented as a witness at the trial. His testimony is discussed, *infra*.

sider them in arriving at its decision.[5] It is one thing for the court to take judicial notice of commonly-known facts. It is quite a different matter for the court to take such notice of opinions such as those of officials of the Canadian Department of Health and Welfare which are not even supported by facts.[6]

It will be shown that the alarming and foreboding assertions of the Government of the dangers of faulty disks are not substantiated factually either by the literature cited or by the testimony at the trial in the District Court. They were originally put forward in the rule-making proceedings of 1960 and 1961 (Pet. Br. 8-9) on the basis of certain complaints referred to in the Government's brief, but without adequate consideration of the following factors.

(1) The physician always has a choice of more than one antibiotic—a "battery" of them, as Dr. Keefer put it (App. 73-74, 120). It is not accurate to imply that the physician relies principally on the disk to select the antibiotic that is "best for administration to his patient" (Pet. Br. 23-24). In addition to the "battery" from which he may choose, the physician has many sources of information to guide him in that choice (App. 76-77), and the location or type of infection, the condition of the patient, the toxicology and pharmacology of the antibiotic, are among the factors upon which he must base the choice. See the discussion in Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, 3rd Ed. 1965, Chap. 56,

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[5] It has long been settled that this court may not properly refer to evidentiary matters not contained in the record certified to the court by the Court of Appeals. *New York Indians* v. *United States*, 170 U.S. 1; *McClellan* v. *Carland*, 217 U.S. 268; *Lawn* v. *United States*, 355 U.S. 339. We know of no exception to this rule applicable to hearsay scientific documents. Compare *New York Indians* v. *United States*, *supra*, where this court held it proper to take judicial notice of statutes or official public documents.

[6] See Note 3, *supra*.

1171 et seq. (Pet. Br. 15). Moreover, as the testimony at the trial and the publications cited by the Government clearly reveal, it is not the physician (clinician) but a laboratory worker who uses the disks.

(2) As all witnesses agreed, it is common practice for the physician to prescribe one or more of this "battery" of antibiotics, on the basis of his experience and the information available to him from various sources, *before* a sensitivity test is run (App. 61, 73, 121, 143-144, Finding Number 8, App. 194). This is "almost always" done according to a Government witness (App. 143-144).

Known antibiotics are classified as to their respective areas of basteriostatic or bactericidal activity and the facts of such classification are well known to physicians. For example, Dr. Weinstein, who wrote Chapter 56 of Goodman & Gilman, *supra*, lists the drug order of choice of 37 antimicrobial agents for use against more than 60 infectious organisms which cause many serious diseases (pp. 1176-1180). Obviously, with this and similar information available, physicians are ordinarily in a position to prescribe antibiotics and, in the vast majority of cases, the prescription will not have to be changed on the basis of a sensitivity test, assuming such a test is run.

The Government notes that the labeling of Bacto-Unidisks states that they are "especially valuable in selecting the drug effective against chronic or persistent infections refractory to primary therapy" (Pet. Br. 11). By "primary therapy" is meant therapy begun *before* a sensitivity test is run, the usual practice.

The statement on page 18 of the Government's brief that batch-testing ". . . is a method of assuring that, when the physician prescribes a particular antibiotic, the patient gets the treatment which the physician intended" is misleading when related to disk-sensitivity testing procedures since (a) initial or primary therapy is almost al-

ways underway when the test results are received from the laboratory and (b) such results are but one of the many sources of information relied upon by the physician. It is quite obvious from the record and the literature cited by the Government that the emphasis in the Government's argument upon the results of the disk test is wholly misplaced. No careful physician would rely so heavily upon such tests which, as Dr. Keefer testified, are the least sensitive quantitatively of the several sensitivity tests available (App. 113).

(3) Dr. Keefer testified that he knew of no public health problem resulting from faulty sensitivity disks and that he had had no experience with the administration of the wrong antibiotic caused by an inaccurate test "because in such instances where such a question may arise, the patient is usually getting one, two, three, and sometimes four different antibiotics if he is desperately ill" (App. 126).

Dr. Truant and Dr. Lerner thought that faulty disks would create a public health problem but both admitted on cross-examination that they could not cite any instance of harm to a patient resulting from the use of a faulty disk in a sensitivity test (App. 93-94, 141). Nor did they even point to a particular instance where faulty disks had affected the validity of the information given to the physician.

Dr. Truant said "I cannot put my finger on it now, but recall that there were a number of instances brought to my attention by individuals in the infectious disease department" (App. 93). If Dr. Truant had been told by "individuals in the infectious disease department" (presumably meaning medical doctors) that his laboratory had given a physician information which misled the physician to a patient's detriment, it is difficult to believe that Dr. Truant would not have remembered the circumstances.[7]

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[7] Dr. Truant did not testify on the alleged health problem until he had completed direct and cross-examination and was recalled.

Petersdorf and Sherris [8] (Pet. Br. 5-6, Note 2) state:

> "Finally it must be emphasized that the course of clinical infections is subject to many more variables than the chemotherapeutic. In our experience, failure of antimicrobial therapy is far more often related to one of these variables than to choice of the incorrect drug. It is not the purpose of this discussion to dwell in detail on the causes for failure of chemotherapy. However, 'choice of the incorrect drug' has been blamed for therapeutic failures all too often, when in actuality failure to relieve a focus of obstruction, to drain an abscess, to ignore evidence of a superinfection or a hypersensitivity reaction, or to attempt treatment of nonbacterial infections, *are the reasons responsible* for unsuccessful chemotherapy. (pp. 775-776, emphasis supplied).

This statement is totally at variance with the frightening prospect of patient injuries resulting from selection of the wrong drug if sensitivity disks are not subject to certification, which has been conjured up by the Government.

The article by Greenberg and Fitzpatrick,[9] cited in support of the argument that uncertified disks are a health hazard shows only that the regulatory agency in Canada agrees with the regulatory agency in the United States. In all of the extra-record citations made in the Government's brief, only in the article by officials of the Canadian regulatory agency have we found the opinion expressed that the result of a test with a faulty disk might be a serious hazard to a patient.

For the reasons herein stated we think it clear that both agencies are wrong, entirely aside from the question of law involved under the Federal Food, Drug, and Cosmetic

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[8] *Methods and Significance of In Vitro Testing of Bacterial Sensitivity to Drugs* 39 American Journal of Medicine 766 (1965).

[9] *Supra*, Note 3 at 383.

Act. Neither the Canadian regulatory officials nor those of the Food and Drug Administration, either in a publication or at the trial in the lower court, have produced a single instance of harm to a patient resulting from the use by the physician of information derived from a disk test or any other factual evidence that hazards are involved in the use of faulty disks. The reason is that it is practically inconceivable that such a thing could happen, with all the built-in protections which we describe herein. Doubtless if we had been given the opportunity to cross-examine the authors of the Canadian publication they, like Dr. Truant and Dr. Wolfe at the trial, would have been unable to document their general statements that a health hazard is involved.

It is of interest to note that in Greenberg, Fitzpatrick, and Branch, *The Status of the Antibiotic Disc in Canada*, 76 Canadian Medical Association Journal 194 at 196 (1957) it is stated that ". . . unless grossly faulty disks are being used, they may still give useful results and may serve to differentiate between highly sensitive and very resistant strains. A careful study of the results in the table will show that because of this feature the majority of discs assayed would probably yield satisfactory tests in spite of their off potencies".

It cannot be doubted that, had the Government found any hard evidence of danger from faulty disks it would have produced it during the six years of this litigation.

It is true that the size of the zone of inhibition can be influenced by the amount of antibiotic on the disk. It can also be influenced equally by other factors, including—

(1) Density of inoculum
(2) Purity of inoculum
(3) pH of medium
(4) Depth of medium

(5) Composition of medium
(6) Temperature and time of incubation
(7) Cleanliness of glassware
(8) Contact of the chemical on the disk with the medium.[10]

All of these factors must be taken into consideration by the technician just as he must consider the variations in the amount of antibiotic substance on the disk.

It does not follow from this, as the Government would have it, that the technician is going to be fooled by variations in zone size (See I-B, *infra*). It does follow, however, that the statements about the public health being threatened by one of the factors involved—the amount of chemical on the disk—have little if any probative value in the absence of documented mistakes related to that factor. Such documentation has never been presented. As Dr. Lerner, a Government witness, said at the trial, ". . . there have been results of tests . . . which I have discarded because they were not coincident with the rest of the information concerning the condition of the patient in question" (App. 141) but, obviously, this is what any careful clinician would do.

(4) The certification regulations of the Food and Drug Administration themselves permit variations of from 67 percent to 150 percent from the potency claimed on the label of the disk (21 CFR 147.1(f)). This is because such variations cannot be avoided. Obviously, therefore, with or without certification there will be variations in

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[10] Gould, *The Laboratory Control of Antibiotic Therapy*, 3 Chemotherapia 477, 478 (1961); World Health Organization Technical Report Series No. 210, *Standardization of Methods for Conducting Microbic Sensitivity Tests*, Second Report of the Expert Committee on Antibiotics (1961), 14-16; *Standardization of Methods for Conducting Microbic Sensitivity Tests*. Preliminary Report of a Working Group of the International Collaborative Study Sponsored by the World Health Organization (November, 1964), 23-25.

zone sizes between different disks containing the same antibiotic substance.

(5) If proper standards and controls are established for the conduct of sensitivity testing and for reading and reporting of results, the laboratory worker will not be misled by a faulty disk. If proper standards and controls are not established and followed he may be misled, with or without certification (I-B, *infra*). This does not mean, however, that the physician will be misled. The disk test result is only one of the many sources of information upon which he relies to form a clinical judgment.

(6) The Government creates the impression that sensitivity tests are routinely run by or on the order of physicians and that all or most antibiotic therapy is based on the results of such tests. This is not a fact. The record reveals with clarity that such tests involve a complicated procedure which can only be followed by trained technicians and that they are conducted in clinical laboratories, primarily hospital laboratories, *after* initial therapy has been begun.

Dr. Keefer said when asked whether it was "customary or rare" for practicing physicians to conduct sensitivity tests: "I would say from the total number of infections that doctors see and treat, both in their offices and in the home, and many in hospitals, the sensitivity test is not used. It is not used routinely". (App. 123).

According to Medical Market Guide (pp. 17, 60, 61)[11] the total sales of antibiotics in the United States in 1967, amounted to $375,175,000. Of this amount $286,631,000 or 77 percent, were purchased on prescription, or by physicians. Both Dr. Keefer's testimony and common experience teach that physicians treating patients outside hospitals do not routinely order sensitivity tests. One

[11] Modern Medicine Publications, 4015 W. 56th St., Minneapolis, Minnesota.

very good reason is that a test is ordinarily not necessary because the initial therapy with a wide spectrum antibiotic is likely to be effective. It is apparent, therefore, that the Government has exaggerated the extent of the use of sensitivity disks far beyond actuality.

B. *Some Improvident Statements in the Government's Brief*

(1) (a) ". . . it became important in medical practice to have a screening test which would provide the physician with an accurate estimate as to which among the several available antibiotics would be likely to be effective against his patient's infecting organism" (Pet. Br. 7).

(b) "Today, approximately 82 percent of the hospitals and clinical laboratories in the United States conduct sensitivity tests prior to the initiation of antibiotic therapy . . ." (Pet. Br. 19).

The quotation in (1) (a), above, implies that sensitivity testing is conducted *before* administration of an antibiotic. The quotation in 1(b) specifically states that this is done in some 82 percent of the hospitals and clinical laboratories in the United States. The first quotation is misleading. The second is untrue (See I-A(6), *supra*) and is not even supported by the Isenberg article cited.[12] The article states at page 186, that in almost 82 percent of "the institutions cultures are taken prior to the initiation of antibiotic therapy." It is perfectly clear that the author was referring to the 66 institutions which answered his questionnaire, not to all institutions in the United States. Moreover, it is obvious that taking a culture prior to the initiation of antibiotic therapy is not the same thing as conducting a sensitivity test. Cultures are taken for many purposes other than

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[12] Isenberg, *A Comparison of Nationwide Microbial Susceptibility Testing Using Standardized Discs*, 1 Health Laboratory Science 185, 186 (1964).

disk sensitivity tests. Moreover, as the testimony shows (*Infra* at II B) the usual order of procedure is (i) taking the culture, (ii) isolation of the organism, (iii) incubation of the isolate, (iv) the sensitivity testing procedure.

It is undisputed on the findings and record of the trial of this case, so studiously neglected in the Government brief, that initial therapy is "almost always" begun before the result of the sensitivity test is received by the physician from the laboratory (App. 143-144). The reason is obvious. The physician can not afford to await the result of a sensitivity test before instituting treatment of an infectious disease.

(2) It is said ". . . a patient's life may well be jeopardized by a disk which contains, *e.g.*, an excess in potency with too rapid diffusion, giving a false reading of sensitivity to that particular antibiotic." (Pet. Br. 21-22). The alleged false reading would, of course, be occasioned by a large zone size, if such a reading should occur. But such a result is remote indeed. It was understood as early as 1956 that "Because of differences in diffusibility, the zone sizes are different for virtually every one of the drugs . . . also, in reading the results it is important for the laboratory worker to understand that sensitivity to each antibiotic is to be considered separately. Once this simple point is grasped and the standards are followed closely, differences in zone sizes have led to no confusion." [13]

The reference in the above quotation to "the standards" is explained by the statements on page 892 and 896 of the article of Kirby et al. that "It is necessary of course, to have a different set of standards [of zone sizes]

[13] Kirby et al., *Clinical Usefulness of a Single Disc Method for Antibiotic Sensitivity Testing*, Antibiotics Annual, 1956-1957, 892 at 894.

for each chemotherapeutic agent, since there are variations in the degree of diffusibility". Standard control cultures of known sensitivity should be included in every test.[14] We have heretofore noted that the regulations of the Food and Drug Administration permit variations of from 67 percent to 150 percent from the potency claimed on the label of the disk (21 CFR 147.1(f)), because variations in the amount of chemical on the disk are unavoidable.

No laboratory technician, with or without certification of disks by the Food and Drug Administration, will know whether his system is operating satisfactorily so that he can detect abnormalities in test results unless he runs controls on his routine procedures. This is true of chemical analyses and serology generally as well as disk tests. Any good laboratory tests and uses cultures (strains) of known sensitivity which yield specific zone sizes under the particular conditions of the test as performed in that laboratory, as a basis for comparison with unknown strains.

The following things are therefore apparent: (a) that, with or without certification, there will be differences in zone sizes both between the various antibiotics (because of differences of diffusibility) and between different disks bearing the *same* antibiotic substance (because of the many variables in the testing procedure and the unavoidable variations in the quantity of the antibiotic substance); (b) that if the laboratory conducting the sensitivity test has not established standards, including that of anticipated zone size, the laboratory worker may be misled with or without certification and, conversely, if the proper controls are used, variations in zone sizes will not mislead him.

Obviously, therefore, an excess of potency would not mislead the adequately trained and properly prepared

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[14] Broadsheet No. 55, The Association of Clinical Pathologists, October, 1966, at 2 and 4.

laboratory technician.[15] He would be suspicious of the larger-than-usual zone size. If there were no zone at all, as was found in some of the tests described in Branch et al.,[16] the physician can simply use another antibiotic since, as Dr. Wolfe, a witness for the Government said at the trial, the physician always has a choice of more than one antibiotic (App. 74) and the test organisms taken from an ill patient are always run with seven or eight or more chemotherapeutic agents.[17] The Bacto-Unidisk itself carries eight such agents and an additional three or four may be placed in the center of the Unidisk.[18] As Kirby et al. said at page 894 (Note 13, *supra*), "... tube dilution tests may be indicated when readings fall in the middle zone or are borderline for other zones. In actual practice, that is rarely necessary." Or, as one authority cited in the Government's brief recommended, if there is no zone at all or if the zone is too large, repeat the test using three or more disks of the same strength.[19] Since in most cases the organism will already have been identified the repeat test can be done in some eight hours.

Moreover, it is essential to understand, as stated by Bauer[20] that "variations in content of high potency discs

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[15] The literature cited by the Government on page 21 of its brief is consistent with these statements.

[16] Branch, Starkey, Power, and Greenberg, *Problems of Standardization of Manufactured Dry Penicillin Sensitivity Disks*, Antibiotics Annual 1956-1957, p. 898 (Pet. Br., Note 19, p. 25).

[17] Bauer, *The Significance of Bacterial Inhibition Zone Diameters, A Study of the Factors Influencing Antibiotic Disc Sensitivity Tests*, Proceedings of Third International Congress of Chemotherapy 466 (1963).

[18] Labeling of Unidisk (App. 184).

[19] Rose and Berky, *A Quality Control System for Disk Antibiotic Testing*, 48 American Journal of Clinical Pathology 200, 203-204 (1967).

[20] Bauer, *supra* at 468.

have negligible influence on zones." This is also true of low potency disks.[21]

(3) It is stated in the Government's brief that "From the presence and size of the clear zones of inhibition around the various discs, the microbiologist is able to advise the physician which of the antibiotics have demonstrated the greatest effectiveness against the infecting microorganism." (Pet. Br. 8). This statement reflects, again, a misapprehension of the function of the disk testing procedure. The results of the tests are *in vitro* only. A reading of the publications cited in the Government's brief establishes beyond any doubt that there can be no such easy and complete translation of the results to *in vivo* effect as is suggested by the quotation and, indeed, as is implied throughout the brief. The physician must take many factors into consideration before using one of the antibiotics to which the test has indicated the microorganism is sensitive.

In the first place, since the patient will, in most cases, already be receiving initial therapy, the likelihood is that the test will merely confirm the physician's judgment (Finding of Fact No. 8, App. 194). Secondly, as stated by Petersdorf and Sherris: [22]

> "It should be clear, however, that the disc producing the largest zone of inhibition does not necessarily

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[21] The regulations of the Food and Drug Administration permit a variation of 2½ millimeters between the diameter of the largest and the smallest zone of a disk of a given labeled potency (21 CFR 147.1(f)). Based on the "standard curve" of potencies set forth in the regulations (21 CFR 147.1(d) this means that the difference between the lowest and highest potencies may be almost 250 percent. Moreover, in three or more consecutive tests 10 percent of the total number of disks tested may have zones which fall outside the prescribed range. In large batches of thousands of disks it seems obvious that the prescribed procedure is not very meaningful.

[22] *Methods and Significance of in Vitro Testing of Bacterial Sensitivity to Drugs*, 39 American Journal of Medicine 766 (1965).

indicate the antibiotic of choice for a given pathogen. For example, if a strain of Esch. coli shows a zone of 22 mm. around a 30 microgram tetracycline disc and a zone of 26 mm. around a 30 microgram chloramphenicol disc, all that can be said is that the strain is susceptible to both compounds. From the agents reported as being effective against the offending organism, the clinician can then select the one most appropriate for therapy. Pharmacologic and toxicologic properties as well as the bacteriostatic or bactericidal actions of the drugs should be considered in making this selection." (pp. 773-774).

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"As with the results of any other laboratory examination, in no case should the zone of inhibition around a paper disk be the sole criterion for selection of a chemotherapeutic, since many other factors must be considered" (p. 777).

These quotations are fair and correct statements. The exaggerated assertion in the Government's brief cannot be reconciled with them.

(4) The references to "potent anti-microbials" and the cautions that their use should be "accompanied by" or "in conjunction with" appropriate "culture and susceptibility" or "sensitivity" testing (Pet. Br. 22-23 and note 17) are entirely consistent with the facts as we have stated them, i.e. that the physician rarely waits for a sensitivity test result before commencing therapy. If he orders such a test at all, the testing procedure would proceed during the primary or initial therapy, as advised in Physicians Desk Reference for Lincocin (lincomycin) and in the prescribing directions of the Food and Drug Administration for chloramphenicol.

The real key to the otherwise portentous references to such drugs as chloramphenicol is the first sentence of the first full paragraph on page 22 of the brief which advises that ". . . the labeling for most of the antibiotics

listed in 21 CFR 145.3 . . . contains directions that the drug is to be used *against known sensitive organisms*, or *after* antibiotic sensitivity testing of the patient's organisms or bacteriologic tests of the sort provided by the sensitivity units." (Emphasis supplied). There are many "known sensitive" organisms as shown by Dr. Weinstein's table of "Current use of Antimicrobial Agents in the Therapy of Infections".[23] Moreover, ". . . the labeling for most of the antibiotics" does *not* as stated by the Government, recommend administration of the drug *after* sensitivity testing. Even in the case of the two examples cited (Lincocin and chloramphenicol) this is not recommended. The statement in question is obviously misleading.

Finally, it must be understood that an inadequate sensitivity test will not cause the physician to administer chloramphenicol. The test will almost always, if not always, show sensitivity of the organism to a number of antibiotics, of which as many as 15 or more may be used in the test. The careful physician will obviously not choose the most dangerous drug (such as chloramphenicol) if there are one or more others to which the organism is sensitive and certainly not if the patient is already responding to the initial therapy. Any prescribing of chloramphenicol without adequate justification, as reported in the press, has certainly not been done on the basis of sensitivity tests.

II.

The Bacto-Unidisk is not a "drug" Within the Meaning of Section 201(g)(1)(B) of the Act

The Government's chief legal argument (Pet. Br. 28 et seq.), in support of its contention that disks are drugs within the statutory definition is that such a construc-

[23] Goodman and Gilman, *supra*, at 1176 et seq.

tion would further the "statutory purpose" of ensuring the safety and efficacy of use of antibiotics and antibiotic sensitivity disks. Such a construction, it is said, would accord "with the settled principle that the Federal Food, Drug, and Cosmetic Act is properly given a broad construction in accord with its purpose to protect the public health" (Pet. Br. 32). The government cites decisions of this court which "emphasize" that "it is within 'the right and the wisdom' of Congress to provide its own glossary of terms and definitions in the Federal Food, Drug, and Cosmetic Act, and . . . the judicial function is to apply what the Congress has written" (Pet. Br. 32). It is also stated that "as the district court acknowledged", sensitivity disks fall within the literal definition of the term drug (Pet. Br. 29-31) and therefore should be construed as drugs to effectuate the statutory purpose. Petitioner concludes that the courts below erred by disregarding both the statutory definition of the term "drug" and the purpose of the statute.

A. *The Remedial Nature of the Statute and The Glossary of Definitions Contained Therein*

1. Congress did indeed provide its own glossary of terms and definitions and this court must apply them in this case.

The statute is concededly remedial and, in the appropriate case, its terms should be given a broad construction in accord with that remedial purpose.

The matter of the remedial purpose of the Act is in fact, however, inapposite to this case. "The courts below did not . . . dispute either the need or the desirability of batch testing of antibiotic discs" (Pet. Br. 28) for the simple reason that no probative evidence of any public health hazard was produced in the case. The only "evidence" was unsupported opinion. The two government witnesses who expressed an opinion were unable to cite

any instance of the wrong antibiotic being administered to a patient because of a sensitivity test using a faulty disk (App. 83-84, 93-94, 140-141), and a witness for Difco Laboratories, Inc. testified affirmatively that he knew of no such public health problem (App. 125-126). The Government was thus unable to convince the lower courts that any public health hazard was involved in sensitivity testing, and now for the first time in this court attempts to create one by a barrage of citations to scientific literature which are *dehors* the record. The literature in question is discussed, *supra*. It does not support the contention that sensitivity disks are "drugs", nor does it justify the Government's dire warnings of danger to the public health.

The Government did not cite *United States* v. *Consolidated Laboratories, et al.*, Civil Action No. 63-C-23, D. Ill., March 29, 1963, also involving sensitivity disks. In that case the Government, as here, attempted unsuccessfully to show danger to the public health and the court found:

> "13a. There is no evidence of injury to the public from the use of the multidisk" (CCH Food, Drug, Cosmetic Law Reporter, Transfer Binder 1963-1967, ¶ 80,030).

It is, therefore, quite clear that no principle of broad construction in the light of the remedial purposes of the statute would justify a decision that sensitivity disks are drugs. As Mr. Justice Frankfurter cautioned in the *Imitation Jam* case (*62 Cases of Jam* v. *United States*, 340 U.S. 593), which is cited by the Government (Pet. Br. 32) in support of its position:

> "In our anxiety to effectuate the congressional purpose of protecting the public, we must take care not to extend the scope of the statute beyond the point where Congress indicated it would stop." 340 U.S. at 600.

2. The Government in its brief announces for the first time that "the more substantial question in this case is how to draw the line between 'drug' as defined in section 201(g) and 'device' which is defined in . . . section 201(h)" (Pet. Br. 29). It would do so on the basis of its "remedial purpose" concept. Similarly, in *Imitation Jam*, *supra*, the question arose as to how to interpret two provisions of the statute, *viz.*, section 403(c) and section 403(g). Adoption of the Government's approach to the manner of distinguishing the two provisions in the instant case would, we submit, "extend the scope of the statute beyond the point where Congress indicated it would stop" (*Imitation Jam*, 340 U.S. at 600). We discuss below the question of whether the disks could be regarded as "devices".

In *Imitation Jam* the government charged that a product labeled "Delicious Brand Imitation Jam" purported to be fruit jam and was misbranded under Section 403 (g) because it did not conform to the ingredient requirements of the standard for that product promulgated under Section 401. The district court, however, held that the product purported to be only an imitation fruit jam in conformance with Section 403(c) and therefore was not misbranded. This court sustained the decision of the district court, holding, as indicated above, that the public health purpose of the statute should not result in an unwarranted distortion of congressional language. To have held the food misbranded the court would have had to determine "that a practice Congress authorized by Section 403(c) Congress impliedly prohibited by Section 403(g)." 340 U.S. at 600.

In the case at bar, the statute defines the terms "drug" and "device" in substantially identical language, as stated by the Government (Pet. Br. 29). Petitioner's outline of the legislative development of the term "drug," and its treatment of the definitions, however, contain a substan-

tive omission. Petitioner states: "Senator Copeland . . . proposed an amendment to add a definition of 'device', parallel to that for 'drug', *but the drug definition was unchanged except for that revision.*" (Pet. Br. 34, emphasis supplied). The emphasized language is not correct; the definition of drug was subsequently revised in S. 5, 75th Cong., 3d Sess., April 14, 1938 (S. Rep. No. 2139) by the addition of the following language at the end of the definition: ". . . but does not include devices or their components, parts, or accessories." The drug definition *was* thereafter unchanged except for that revision.

The Government's brief ignores this excepting clause; *e. g.*, in a footnote on page 31, petitioner states that the Canadian Food and Drug Act "defines 'drug' and 'device' in language similar to that involved in this case." In fact, the pertinent portions of the Canadian definition of "drug" and "device," relating to diagnosis and treatment, are identical. The important factor is the absence in the Canadian law of a clause excepting devices from the definition of drug. The point is a significant one. Without the excepting clause an article could be both a device and a drug if its intended use fell within the statutory criteria. Thus, if sensitivity disks were intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, they could be classified as both drugs and devices and the Government would not be placed in the awkward position of attempting to ignore the fact that Section 201(g)(1) excepts devices from the definition of drug.

It should be noted that of the four basic jurisdictional definitions (foods, drugs, devices and cosmetics) in the statute, only that for drugs excludes other articles (devices) from its operation (the exclusion of soap from the definition of "cosmetic" is obviously not here pertinent). For example, articles may be and frequently are classified under the Act as both foods and drugs or as cosmetics and drugs depending upon the

representations made for them. See, *e.g.*, 33 F. R. 9352, where the Food and Drug Administration classified certain salt substitutes as both foods and drugs under the Act. It must be presumed that Congress in excepting devices from the drug definition did not engage in an idle act.

If, therefore, the court should adopt the Government's approach it would in effect be repealing that part of Section 201(g)(1) which excepts devices from the drug definition, and "extending the scope of . . . [of that provision] beyond the point where Congress indicated it would stop" (*Imitation Jam*, 340 U.S. at 600). This result would be analogous to that which would have occurred had the Court adopted the position urged by the Government in *Imitation Jam*, i.e., when the Food and Drug Administration has promulgated a definition and standard of identity for a food under Section 403(g), Section 403(c) is thereby deprived of any legal effect.

3. The Government urges as an approach to the problem of drawing the line (Pet. Br. 29) between drug and device, that adopted by the Court in *AMP, Inc.* v. *Gardner*, 389 F. 2d 825, cert. denied sub nom. *Amp, Inc.* v. *Cohen*, No. 86, this term, October 14, 1968,[24] i.e., to apply the Act "functionally to afford the public the protections of the statute" (Pet. Br. 33), and to reject "the idea that this important public law is 'restricted to products commonly called 'drugs'" (Pet. Br. 32). We show in Part II B, *infra*, that the action of the lower courts in this case in resorting to medical testimony to elucidate the meaning of the language in the statutory definitions was an approach which was proper and in accord with well-known principles of statutory interpretation enunciated by this Court. The AMP approach as interpreted by

[24] See discussion, *infra* Part II D.

the Government [25] would result in application of the definition of drug to any article, including devices, where, in the opinion of the Food and Drug Administration, the more restrictive requirements of the statute relating to drugs, new drugs and antibiotic drugs would protect the public. This is neither an orderly nor a legally justifiable way of determining the coverage of a statute. It ignores the exclusivity of the definition of drug in Section 201 (g) (1). It offers no standard for determining the delimitations of the definition of drug.

An even more basic evil lurks in the Government's interpretation of the *AMP* approach to the distinction between drug and device. The Federal Food, Drug, and Cosmetic Act is a stark, liability-without-fault, criminal statute.[26] As stated by Mr. Justice Frankfurter in *Dotterweich*,[27] a case involving criminal prosecution of a corporation president for violation of the Act:

> "The prosecution to which Dotterweich was subjected is based on a now familiar type of legislation whereby penalties serve as effective means of regulation. Such legislation dispenses with the conventional requirement for criminal conduct—awareness of some wrongdoing. . . . Hardship there doubtless may be under a statute which thus penalizes the transaction though consciousness of wrongdoing be totally wanting." (320 U.S. at 280-281, 284).

The Government in effect would have this Court lay down the following "standard" by which a businessman,

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[25] It is not necessary for this Court to adopt the vague, open-end approach urged by the Government as the basis for the result in *AMP*. As indicated in Part IID, *infra*, the article involved in AMP is composed of a material recognized as a drug in the United States Pharmacopeia, and therefore is arguably a drug under the statute (Section 201 (g) (1) (A)).

[26] Section 303.

[27] *United States* v. *Dotterweich*, 320 U.S. 277; see also *United States* v. *Wiesenfeld Warehouse Company*, 376 U.S. 86, 91.

at the risk of criminal prosecution if he be wrong, must determine whether his product is a drug or device: whether the statutory purposes of protecting the public would be served by his classification of the product. In order to make this determination, the businessman would have to resolve two questions: (1) whether in his opinion based on his knowledge of the product, the statutory purpose of protecting the public would be served by his decision; and (2) whether the Food and Drug Administration would agree with that decision. If he decides the product is a device and thereafter proceeds with production and the Food and Drug Administration concludes that the product is a drug, he may be subjected to criminal prosecution on at least five counts [28] and, if convicted, to imprisonment for five years or a fine of $5000 or both such imprisonment and fine (21 USC 333(a)). This result could follow regardless of any "consciousness of wrongdoing", as noted above.[29]

It is submitted that the *AMP* approach as interpreted by the Government (Pet. Br. 32-33) would result in an unconstitutionally vague application of the statute which would not enable a person subject to its terms to determine in advance whether his conduct will be considered criminal. As stated by this Court in a case in which defendant had been charged with evading the provisions of a price regulation promulgated by the Price Administrator pursuant to the Emergency Price Control Act of 1942, the law "must adequately inform those who are subject to . . . [it] what conduct will be considered evasive so as to bring the criminal penalties of the Act into

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[28] Section 301(d), (f), (p) and Section 301(a) based on various adulteration or misbranding charges in violation of Sections 501 and 502.

[29] In case of a violation with intent to defraud or mislead, the penalty could be imprisonment for three years or a fine of $10,000, or both such imprisonment and fine.

operation. . . . The dividing line between unlawful evasion and lawful action cannot be left to conjecture. The elements of evasive conduct should be so clearly expressed . . . that the ordinary person can know in advance how to avoid an unlawful course of action." *M. Kraus and Bros. Inc.* v. *United States*, 327 U.S. 614, 621-622 (1946).

In the instant case a person subject to the Act must know how to distinguish a drug from a device on the basis of substantially identical statutory definitions of those terms, i.e., is the article intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease. The only differences between the two definitions, insofar as here pertinent, are that Section 201(g)(1) excludes devices from the definition of drug, and Section 201(h) defines "device" in terms of instruments, apparatus and contrivances. As indicated above, the approach in *AMP*, as interpreted by petitioner, would in effect expunge these two differences from the definitions, with the result that the definitions would provide no clue whatever as to the meaning of drug and device. It is submitted that the distinction between drug and device would under the government's approach be "left to conjecture" and this criminal statute with its severe sanctions can not be constitutionally so applied. The same considerations are not present when the question to be determined is whether an article is a food or a drug or a cosmetic or a drug since the definitions of food, drug, and cosmetic do not contain such substantially similar language as do the definitions of drug and device.

B. *The Statutory Definition of "Drug" as Applied by the Lower Courts*

1. It is stated in the Government's brief (p. 29) that despite a contrary suggestion by the court of appeals, the disks fall within the literal definition of drug as articles intended for use in the diagnosis, cure, mitigation, treat-

ment or prevention of disease. The statement will not stand examination. It is beyond cavil that the word "treatment" as used in Section 201(g)(1)(B) means "treatment of a patient". It seems quite obvious that a disk used only as part of a test procedure in a laboratory is not used in the treatment of a patient.

The Court of Appeals held that the Bacto-Unidisk "has nothing to do with diagnosis or prevention of disease"; that "it is not intended for use either internally or externally to cure, mitigate, or treat disease"; and that "it only aids the physician to determine what antibiotics to use for the cure, mitigation or treatment of disease" (App. 200).

This is in accordance with the evidence. It is clear that the *information* obtained from the *sensitivity test* (not just from the disk) is used as a guideline to treatment of some cases of disease (App. 48, 56, 99, 104). The testimony fully supports the statement in Finding of Fact Number 8 (App. 194) that: "The information obtained from the sensitivity testing procedure outlined in Finding Number 7 is used by the physician as a guideline to treatment of the patient . . ."

No witness would accede to the Government's suggestions that the disk itself was used, or intended for use, in treatment, and the Government has abandoned that approach in this Court (Pet. Br. 29). Instead it states that "as a result of information as to the inhibiting action of the particular drug on the patient's particular infectious micro-organisms, the infection is diagnosed as one sensitive to a particular antibiotic, and the patient is treated with that particular drug" (Pet. Br. 29). This statement, however, is fraught with error. It implies that before treating a particular patient with a particular antibiotic for a particular infection, the physician awaits the results of a sensitivity test to see what antibiotic will inhibit the particular organism. The practice

of physicians is to the contrary, as all witnesses agreed (App. 60-61; 120-123; 143-144; Finding of Fact Number 8, App. 194). It is absurd to say that the infection is "diagnosed" as sensitive. The term diagnosis, as noted by petitioner (Pet. Br. 30) is a statutory term of art, and the statute speaks of *diagnosis of disease*, not diagnosis of the susceptibility of a pathogen to a drug.

"Diagnosis", Dr. Keefer testified, "is the recognition of disease or illness. That is the general medical term or interpretation of the term—recognition, identification of illness. . ." (App. 118). The disease cannot be recognized (diagnosed) until the suspected organism has been identified and "the disk does not enable one to identify an organism" (App. 118). Where the disk test is used, the first step is the identification of the organism; the second is the disk test. Dr. Keefer was asked: "If you skip that step, Doctor, [identification] and went right to the disk test, could you make a diagnosis?" He answered: "Could not make a diagnosis" (App. 119).

Finding of Fact Number 7 (App. 193) plainly states that the step of identification of the organism is preliminary to the sensitivity testing procedure. This finding also describes the information yielded by the test, i.e., an indication of whether the test organism is sensitive or resistant to the chemical on the disk. It is not logical to consider that information as a part of diagnosis or recognition of a disease condition. It is suggestive of the kind of treatment which may be appropriate but it is not suggestive of what disease condition is involved. The testimony lends no support to the contention that the disk is used in diagnosis.

Moreover, Finding of Fact Number 8 (App. 194) makes it clear, with respect to the information obtained from the sensitivity test that: "The disk, the culture medium, the Petri plate, and the incubation are all a part of the testing procedure yielding this information"; that "such in-

formation could not be obtained from the disk itself"; and that "the test is only one of many sources (such as the physician's experience, clinical symptoms, the literature, and other tests such as urinalysis and blood serum tests) of the information upon which the physician relies in determining the treatment to be administered". It is thus apparent that if the disk is a "drug", so are the culture medium, the Petri plate, and the incubator, as well as the medical literature and materials used in other tests such as urinalysis and blood serum tests (and others employing body specimens).

The District Court found that—

> "In medical science those substances which are for administration to or for use on, a person for the treatment of disease or injury, are regarded as drugs (Tr. 102-103, 195, 199, 261-262, 283). This is the commonly accepted view of physicians generally. A physician who testified for the libelant could think of no example of a substance not taken into or applied to the body which he would 'consider medically' as a drug (Tr. 103)". (Finding Number 9, App. 194).

The Court also found that "The article does not purport to be and is not represented as a 'drug' as that term is used in medical science or by physicians generally. It is labeled 'For Laboratory Use . . .'". (Finding of Fact Number 11, App. 195).

These findings are fully supported by the record and are not challenged by the Government. They lend powerful support to the clear purport of the testimony that the disk is not used in the diagnosis or treatment of disease.[30]

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[30] The definition of "drug" in Dorland (Pet. Br. 30, Note 27) is plainly limited to substances "for the relief of pain or suffering, or to control or improve any physiological or pathological condition." All of the preceding portions of the definition are modified by the portions quoted. Moreover, Stedmans Medical Dictionary (21st Ed. 1966), Blakiston's New Gould Dictionary (2nd Ed. 1956), Butterworth's Medical Dictionary (1965), and Webster's New International Dictionary, all define "drug" as a medicine. This is entirely consistent with Dorland.

The Bacto-Unidisk is a laboratory reagent. There are more than 150 pages in the United States Pharmacopeia (and others in the National Formulary) describing hundreds of laboratory reagents or testing materials for use in making the various tests and assays described in the Pharmacopeia.[31] If the Government's position that sensitivity disks are used in the treatment of disease or in the diagnosis of an infection were sound, the Food and Drug Administration could, on the basis of the same approach, classify many, and perhaps most, of those reagents as "drugs" under the statute.

There is absolutely no warrant for the extension of jurisdiction over these laboratory tools, either in the statute or its legislative history. The proper forum for the Administration to advocate the subjection of sensitivity disks to the Act is the Congress. If the Administration can present a serious basis for statutory coverage of disks it will, as it has heretofore, receive the attention of the national legislature. Instead, during the six years of this litigation, the spectre of danger to health has been repeatedly flaunted without the production of any data to support it.

If the Government's position were sound the disk could legally be represented in its labeling as suitable for the treatment of disease; for example, "for use in the treatment of bacterial infections." Such a statement would obviously be false and would constitute misbranding under Section 502(a) of the Act, under which a drug is deemed to be misbranded "if its labeling is false or misleading in any particular."

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[31] These reagents are not regarded as drugs by the Committees on Revision of the official compendia (Sec. 201(j), 21 U.S.C. 321 (j)) and therefore do not appear in the monograph section of the compendia. Thus, they are not "recognized" in the sense of Sec. 201(g)(1)(A). (App. 153-154; 155-157; 167-171).

2. The Courts below were not in error, as suggested by petitioner (Pet. Br. 32) in "their application of . . . the common medical usage of the term drug" to the statutory definition of that term. The statute does contain its own definition of "drug", thereby making that word a term of art (Pet. Br. 30). The applicable portion of the definition is, however, composed of words having a technical meaning, i.e., "diagnosis, cure, mitigation, treatment or prevention of disease." Recognizing this fact, *both petitioner and respondent* presented evidence by medical and scientific witnesses as to the meaning of the word "drug" in terms of the statutory definition, and its application to sensitivity disks, and specifically as to the meaning of the terms "diagnosis" and "treatment". In receiving such evidence, the trial court was following a long-established principle of statutory construction set forth by this Court in a number of cases, *viz.*, resort to expert evidence *aliunde* in order to give meaning to technical statutory language. *Binns et al.* v. *Lawrence*, 53 U.S. 9; *Boston Sand & Gravel Co.* v. *United States*, 278 U.S. 41; *National Labor Relations Board* v. *Coca-Cola Bottling Co.*, 350 U.S. 264. If terms such as "diagnosis" and "treatment" are not to be given the meanings ascribed to them by physicians, where, as here, no legislative history explains them, the courts are left with no expert advice on the matter at all.

Petitioner agreed at the trial that the experts were of help to the Court in this matter (App. 105). Petitioner cannot now ignore the testimony of its witnesses and respondent's as to the meaning of the terms "diagnosis" and "treatment" and the word "drug". Even if the finding of the District Court that the term "drug" is limited to substances administered or applied to patients were entirely ignored, we submit that the evidence shows that the disks are nevertheless not "drugs" because they are not used in "diagnosis" or "treatment", as the testimony and findings show.

Securities and Exchange Commission v. *Ralston Purina Co.*, 346 U.S. 119 (Pet. Br. 29-31) is inapposite. There, the offering of securities with respect to which no registration statement was in effect was clearly within the statutory prohibition *unless* it was exempt as "not involving any public offering". The Court, following established principles, placed upon the issuer of the securities the burden of proof of showing that the offering fell within the exemption. The issuer was unable to meet the burden. Here, in contrast, the burden of proof was upon the government to establish that Bacto-Unidisks were "drugs". It failed to do this and now offers its frail public health argument as a basis for overturning the findings and decisions of the lower courts.

C. *The Memorandum Opinion of the District Court*

The Government makes the statement, and relies upon it, that the district court ". . . acknowledged (App. 190) that the discs fall within the literal definition of 'drug' in Section 201(g) . . ." (Pet. Br. 29, 30, 33).

It is clear, however, as shown above that it is not the disk (the "article" seized) but the *information* obtained from the sensitivity testing procedure as a whole, which is used as a guideline to therapy, and that such information does not in any sense constitute a "diagnosis" of the patient's infection.

It is well-established, moreover, by decisions of this Court, that an appellate court may not refer to a memorandum opinion of a District Court sitting without a jury, for the purpose of impeaching that court's formal findings of fact; or, as this Court stated it "for the purpose of eking out, controlling, or modifying" such findings. *Stone* v. *United States*, 164 U.S. 380, 383 (1896); *Saltonstall* v. *Birtwell*, 150 U.S. 417 (1893); *United States* v. *Shoshone Tribe of Indians*, 304 U.S. 111, 115 (1938); *M. E. Blatt Co.* v. *United States*, 305 U.S. 267, 277

(1938). Where no part of the memorandum opinion is regarded by the trial court as a finding of fact, statements contained therein cannot be utilized on appeal to refute or negate findings of fact expressly made by the court. *General Metals Powder Co.* v. *S. K. Wellman Co.*, 157 F.2d 505, 509, cert. denied 329 U.S. 812, rehearing denied 330 U.S. 854.

It seems perfectly clear in the instant case that the trial court's memorandum opinion did not and was not intended to contain findings of fact. On the contrary, the court invited the parties to submit findings of fact and conclusions of law. The subsequent adoption by the court of detailed formal findings of fact and conclusions of law after proposed findings and conclusions were submitted by counsel is conclusive evidence of the court's intention with respect to the memorandum opinion and brings the case within the above-cited case authorities.

Moreover, an appellate court may not set aside the findings of fact of the trial court unless they are found to be "clearly erroneous". They are not clearly erroneous unless the reviewing court, on the entire evidence, is left with the definite and firm conviction that a mistake was committed. *United States* v. *United States Gypsum Co.*, 333 U.S. 364, 395, rehearing denied 333 U.S. 869 (1948); *Commissioner of Internal Revenue* v. *Duberstein*, 363 U.S. 278, 291 (1960); *S. C. Johnson & Son, Inc.*, v. *Johnson*, 266 F. 2d 129, 142-143 (6th Cir., 1959), cert. denied, 361 U.S. 820. It is not enough that the appellate court might give the facts another construction or resolve the ambiguities differently. *United States* v. *National Association of Real Estate Boards*, 339 U.S. 485, 495-496 (1950).

The burden of proof is upon the Government to prove to the appellate court that the trial court's findings and conclusions are clearly erroneous, *S. C. Johnson & Son, Inc.* v. *Johnson, supra*, at 143

In a recent decision the Court of Appeals for the Sixth Circuit emphasized that Rule 52(a) is not a purely arbitrary rule but a well-established, frequently applied, principle of law. *Krumholz* v. *Good*, 318 F. 2d 911, 912 (6th Cir. 1963).

The Government in its brief in the court of appeals and here has largely ignored the formal findings of fact and conclusions of law of the District Court and has made no effort to sustain its burden of proving that the trial court's findings and conclusions are clearly erroneous as required by *Johnson, supra.*

Obviously, therefore, the Government may not undercut the court's formal findings of fact by use of a statement in the Memorandum Opinion. Moreover, in the formal conclusions of law of the court (Number 4, App. 196) it is stated that —

> "The seized article does not purport to be nor is it represented to be a drug within the meaning of 21 U.S.C. 321(g). It is not intended for drug use (See Findings Numbers 9 and 10) and it is the intended use which determines its status under that Section . . ."

D. *AMP, Inc.* v. *Gardner*

As above indicated, petitioner urges that this court in distinguishing between drug and device adopt the government's interpretation of the approach taken in *AMP, supra, viz.*, that the statute should be "applied functionally to afford the public the protections of the statute" (Pet. Br. 33) and is "not restricted to products commonly called 'drugs'" (Pet. Br. 32). *Bradley* v. *United States*, 264 Fed. 79, is also cited to support the latter point.

The purpose of noting that the Act is not restricted to products commonly called drugs or to dictionary or pharmacopeia definitions is obscure, since nobody to our knowledge disputes the proposition that it is the "intended

use" of the product which determines whether it is a drug (i.e., whether it is for use in the diagnosis or treatment of disease) and the Court of Appeals specifically recognized that principle in the instant case (App. 201). That is why spring water is a "drug" if it is recommended for use in the treatment of disease. *(Bradley* v. *United States, supra).* Obviously therefore we do not urge and the court below did not hold, that the Act is restricted to products commonly called drugs. The effect of the decisions below was that, since the Bacto-Unidisk was neither held out for the diagnosis or treatment of disease nor used in or on the body it was not a "drug" under the statute.

In its Brief in Opposition to the Petition for Certiorari in *AMP* the Government states with respect to the suture material there involved (p. 7):

> "The essential element, nylon suture material, is recognized as a drug in the official United States Pharmacopeia and therefore is squarely within that portion of the statutory definition which defines as drugs 'articles recognized in the Official United States Pharmacopeia.' Cf. *United States* v. *48 Dozen Packages . . . of Gauze Bandage,* 94 F. 2d 641 (C.A. 2)".[22]

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[22] Section 201(g), the definition of "drug", is composed of three clauses: Clauses (A) defines drug in specific terms, *viz.*, articles recognized in the official compendia; clauses (B) and (C) define drug in general language which would include the drugs in the compendia, *viz.*, articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or intended to affect the structure or function of the body. It is submitted that due to the manner in which the term is defined in the statute, the rule of *ejusdem generis* is applicable. Under that rule, sensitivity disks would not be considered drugs since they are not recognized in the official compendia, and are not "of a kind with" articles which are recognized in the compendia. See *United States* v. *48 Dozen Packages . . . of Gauze Bandage,* 94 F. 2d 641 (2d Cir. 1938). Judge Thornton found as a fact that based on the testimony adduced at the trial, disks are not the kind of articles which are accepted for admission to the official compendia (Finding No. 9, App. 194).

Moreover, the Brief in Opposition in *AMP* (pp. 8-9) notes that, unlike the disks, the article there involved enters the surgical wound and part of it remains in the body. It also points out (p. 7) that the article is used to ligate or tie off bleeding blood vessels during a surgical operation and that, therefore, it affects the structure or function of the body within the meaning of Section 201 (g) (1) (C).

It is fully apparent therefore that there are both legal and factual differences between the instant case and *AMP*, and the Government so states in its Brief in Opposition in *AMP* (pp. 8-9). Even more conclusive, however, is the fact that the manufacturer of the product in AMP, unlike Difco Laboratories, did not dispute the proposition that its product was subject to the Act (either as a drug or as a device) and, in the language of the court of appeals, "proceeded to comply with the requirements of the Act relating to devices" (389 F.2d at 826).

It was conceded, therefore, that the product in AMP was "intended for use in the diagnosis, cure, mitigation or treatment of disease" or "intended to affect the structure or function of the body", or both, since it would not be a device under Section 201 (h) unless it was intended for one of more of such uses. The language relating to diagnosis and treatment (Section 201 (h) (1)) and that relating to affect upon the structure or function of the body (Section 201 (h) (2)) are common to the definitions of "drug" and "device". The very question in the Bacto-Unidisk case is whether the disk falls within the provision of Section 201 (g) (1) which corresponds to Section 201 (h) (1), *viz.*, Section 201 (g) (1) (B), relating to diagnosis and treatment.

It is obvious, therefore, that the "broad construction" given to the Act in *AMP* is not comparable to that which the Government is seeking with respect to Bacto-Unidisks.

In the former the basic jurisdictional test was concededly met and the question was only one of classification as between "drug" and "device". In the latter the testimony at the trial shows that the basic jurisdictional test, *viz.*, whether the disk is used in the diagnosis or treatment of disease, is not met. In addition, the possible dangers involved in incorporation of a substance into the human body are obviously not present in the case at bar.

III.

The Certification Provision (Section 507) is Not Applicable to Articles Not Administered or Applied to Patients.

It is stated by the Government that the only substantive question in the case is whether the Bacto-Unidisk is a "drug" (Pet. Br. 10). This is not correct. We have consistently pointed out that, even if the article were held to be for use in the "diagnosis" or "treatment" of disease and therefore held to be a "drug" under Section 201(g)(1)(B), it is not for administration or application to patients and therefore is clearly not subject to certification under Section 507. This is clear from the legislative history of Section 507 which is recited in part in the Government's brief.

The Government fails to point out that (1) when section 507 was enacted in 1945 no sensitivity disks were being produced commercially and Congress had never heard of such articles, (2) the language of section 507 and portions of the legislative history unmentioned by the Government clearly show that the concern of the Food and Drug Administration and Congress was to protect patients from the administration of an antibiotic drug (penicillin) which was not safe and efficacious for such administration without stringent controls.[33] This purpose

[33] S. Rep. No. 410 and H.R. Rep. No. 702, 79th Cong., 1st Sess. (1945).

—to protect patients receiving antibiotic drugs—was not changed in 1947, 1949, or 1961.[34]

The quotation from the testimony of Secretary Ribicoff (Pet. Br. 16-17) is obviously applicable only to antibiotics administered to patients. The phrase "Since they are employed in conditions where even minor delays in effective treatment may result in death . . ." used by the Secretary could not be applicable to sensitivity disks by any reasonable interpretation since, by its very nature, the disk test involves substantial delay.

In a letter to the President of the Senate the Federal Security Administrator[35] said that the drugs being added to the certifiable list in 1949 were "highly efficacious for one or more serious diseases", such as rickettsial diseases, atypical pneumonia, and virus diseases.[36] Obviously the Administrator was talking about drugs to be used for administration to patients.

In 1962 Section 507 was amended to extend certification to all antibiotics "intended for use by man" (as distinguished from veterinary use).[37]

The words "intended for use by man" and "for human use" are used interchangeably throughout the several committee reports on the bills which became the Drug Amend-

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[34] *E.g.*, S. Rep. No. 600, 81st Cong., 1st Sess. (1949), 1949 U.S. Code Congressional Service 1530-1531.

[35] The predecessor of the Secretary of Health, Education and Welfare.

[36] Op. cit. supra., S. Rep. No. 600, U.S. Code Congressional Service at 1531, 1532.

[37] Drug Amendments of 1962, P.L. 87-781, 76 Stat. 780, Sec. 105 (a), amending Section 507(a).

ments of 1962.[38] In the context, they quite clearly refer to use for administration to man by ingestion or otherwise. Thus, the uses of sensitivity disks are clearly excluded, whether the organism being tested by the disk is from man or animal.

The Department or Health, Education and Welfare, under date of October 10, 1962, released a document entitled, "Drug Amendments of 1962, Federal Food, Drug and Cosmetic Act—Summary", which is explicit. It states under "Batch Certification of Antibiotics" that:

> "14. All antibiotic drugs to be *administered to humans* are made subject to batch-by-batch testing and certification by FDA for identity, strength, quality, and purity to assure that they "are safe and effective before they are released for sale." [Emphasis supplied].[39]

Sensitivity disks, of course, are not "administered" at all. It is evident, therefore, that the Congress, in extending certification authority in the 1962 amendments, and limiting it to antibiotics administered to human beings, was following the pattern established by Section 507 as originally enacted and as reflected in its legislative history.

Moreover, it seems quite clear that the concept of "safety of use" is applicable only to dosage forms of substances which are administered to patients. This is the clear pattern of the statute. Thus, "safety of use" is a statutory test of pre-marketing clearance of a "new drug" under Section 505 of the Act. It clearly refers

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[38] S. Rep. No. 1744, Parts I (July 19, 1962) and 2 (August 21, 1962), 87th Cong. 2d Sess., on S. 1552, p. 19 (Part I) and p. 9 (Part 2); H.R. Rep. No. 2464, 87th Cong., 2nd Sess., p. 11 (1962); H.R. Conference Report No. 2526, 87th Cong., 2d Sess., on S. 1552, p. 21 (1962). Part I of the Senate Report and the Conference Report are set out in U.S. Code Congressional and Administrative News, Vol. 2, 1962, at pp. 2884 and 2927.

[39] A subsequently issued printed pamphlet entitled "Summary of the Drug Amendments of 1962" repeats this statement on page 6.

to safety for application or administration to patients.[40]

The concept of safety of use is inapplicable to sensitivity disks, since they are not applied or administered to the patient. It seems clear, therefore, that, even if they were drugs, they would not be subject to certification under Sec. 507.

The same is true of one of the most important of the original provisions of the statute, Section 502(j), under which a drug is deemed to be misbranded "if it is dangerous to health when used in the dosage or with the frequency or duration prescribed, recommended or suggested in the labeling thereof". This provision patently applies to drugs in dosage forms for administration to individuals and not to laboratory reagents such as sensitivity disks.

It seems apparent therefore that even if the sensitivity disks were drugs, they would not be the kind of drugs which are subject to certification.

IV.

If the Bacto-Unidisk Were Subject to the Federal Food, Drug, and Cosmetic Act it Should be Classified as a Device

The suggestion was offered to the lower courts on behalf of respondent that, if the Bacto-Unidisk were subject to the Act at all (respondent contends it is not), it should be treated as a device within the meaning of Sec. 201(h). As a device it would not be certifiable.

The only difference between a drug and a device insofar as the definition of "device" and the pertinent por-

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[40] See, e.g., Report of Special Committee to Review the Policies, Procedures, and Decisions of the Division of Antibiotics and the New Drug Branch of the Food and Drug Administration (approved September 27, 1960); and analysis of H.R. 11581, 87th Cong., 2d Sess., by Department of Health, Education and Welfare, Hearings before the Committee on Interstate and Foreign Commerce, House of Representatives, 87th Cong., 2d Sess., on H.R. 11581 and H.R. 11582 (p. 23).

tion of the definition of "drug" (Section 201(g) (1) (B)), are concerned, is that devices are "instruments, apparatus and contrivances" and drugs are articles other than instruments, apparatus, and contrivances.[41]

Sensitivity disks are logically classified as "instruments, apparatus, or contrivances, "if they could be regarded as used in the "diagnosis" or "treatment" of disease. As the testimony shows, there is nothing in the nature or manner of use of reagent disks to justify a holding that they are used in "diagnosis" or "treatment" and, of course, they are not used in or on the body. They therefore logically fall neither within the definition of "drug" nor that of "device". It is, however, somewhat less difficult to conceive of them as "devices" because they are in fact a "means" or "appliance" within the dictionary definition of the term.[42]

A "generator" supplying chlorine gas for *inhalation* by patients to treat arthritis and sinusitis was considered by the Food and Drug Administration and treated by the Court as a "device" in *United States* v. *22 Devices . . . Halox Therapeutic Generator*, 98 F. Supp. 914 (D. Cal. 1951).

A so-called cancer diagnosis kit with two bottles of common chemicals (one of which was ether, a substance commonly used as a drug), which were to be added to a sample of the patients urine to determine whether cancer

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[41] The last clause of Section 201(g) (1) expressly provides that the definition of "drug" does not include devices.

[42] The pertinent definitions in Webster's New International Dictionary are as follows: Device: "1. That which is devised, or formed by design; a contrivance; an invention. . ." Instrument: "1. That by means of which any work is performed or result is effected; a medium; means." Apparatus: ". . . Specif. Any complex instrument or appliance, mechanical or chemical, for a specific action or operation. . ." Contrivance: ". . . 3. A mechanical device; an appliance."

was present, was considered to be a "device" and an injunction was granted against its shipment.[43] Likewise, a radio diagnostic and treatment machine which was held forth as requiring only a drop of the patient's blood for diagnosis and treatment of various disease conditions, was considered by FDA as a "device", not a drug. The device was seized and a criminal prosecution was brought against its shipper.[44]

It seems manifest that if the disks are drugs because their use involves the testing of organisms from the patient as an aid in deciding upon the proper treatment, the last two devices above described likewise fall into that category. In fact, however, it seems clear that none of the three articles is a drug.

The World Health Organization Technical Report Series No. 210, cited in the Government's brief (p. 21) states, at page 13 that "It is desirable that each government should ensure some system of control over the quality and particularly the antibiotic content of such commercially prepared discs" and that "It is necessary that batches from each manufacturer should be tested from time to time . . ." To the same effect is the Government's brief, pp. 20-21.[45]

We have above noted that, if sensitivity disks are subject to the Federal Food, Drug, and Cosmetic Act, they must fall within the definition of "device" in Section

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[43] Annual Report of the Food and Drug Administration, 1953, Kleinfeld & Dunn, Federal Food, Drug and Cosmetic Act, 1953-1957, p. 650.

[44] Annual Report, Food and Drug Administration, 1950, Kleinfeld & Dunn, Federal Food, Drug and Cosmetic Act, 1953-1957, pp. 575, 624.

[45] The brief implies that a dessicant is required by regulation. The regulations do not, however, require the use of a dessicant (21 CFR 147.2(b)). They leave it to the manufacturer to decide whether it is needed.

201(h). If, contrary to our view the disks are regarded as devices they could be subjected, as suggested by the Technical Report, to "some system of control" under the provisions of Sections 501 and 502 relating to the adulteration and misbranding of devices. A disk would be adulterated under Section 501(c) " if it did not contain the amount of antibiotic substance stated on the label. Thus, if the claimed potency of tetracycline were 10 micrograms and only 2 micrograms were present, the disk would be adulterated. Likewise, it would be misbranded under Section 502(a). The labeling would also have to bear adequate directions for use under Section 502(f).

Under its inspection and sampling programs the Food and Drug Administration could, as the Technical Report suggests, test batches of each manufacturer's disks "from time to time".

It is stated in the brief for the Government that there is need for an expiration date on the label of the disks. This matter could readily be handled under Section 201(n) of the Act. There can be no reasonable doubt that manufacturers of disks would comply if they were advised by the Food and Drug Administration that representation in the labeling of the amount of antibiotic in a disk would be misleading unless the labeling stated an expiration date because it "fails to reveal facts material in the light of such representations [as to potency of antibiotic substance] or material with respect to consequences which may result from the use of the article to which the labeling relates under the conditions of use prescribed in the labeling thereof" . . ." (Section 201(n)).

We have referred to the built-in protections against the possibility of erroneous information from a sensitivity test resulting in harm to a patient in the absence of any government control. There need be no apprehension to-

day that manufacturers would fail to label disks with an expiration date if there were no controls whatever. Manufacturers know that the laboratories which use disks want an expiration date and could not avoid including it in the labeling even if they were minded to do so. It is emphasized, however, that sensitivity disks are used neither to diagnose a disease nor to treat or prevent it. The information derived from them is at most an aid in determining whether the initial therapy should be continued. The disks are therefore distinguishable even from the alleged uses of the devices which have been described.

V.

The Legal Conclusion of the Commissioner of Food and Drugs that Sensitivity Disks are "Drugs" is Subject to Attack in this Proceeding

The Government in its brief states that it does not challenge respondent's right to question in a libel for condemnation proceeding, the legality of the determination of the Commissioner of Food and Drugs that antibiotic sensitivity disks are drugs (Pet. Br. 10). It does, however, point out that respondent did not seek "judicial review of the promulgating order as authorized by 21 USC 357(f) and 371(f) . . ." (Pet. Br. 9), and emphasizes that the Commissioner's determination was made "in a rule-making proceeding" (Pet. Br. 14).

Respondent has challenged no regulation in this proceeding, for there is, in fact, none applicable to the Bacto-Unidisk. Bacto-Unidisks contain sulfadiazine, which is not an antibiotic substance. Both the administrative determination that sensitivity disks are certifiable antibiotics and the regulations [46] pertaining to certification of disks apply only to disks containing antibiotics. Respondent, therefore, is attacking the legal conclusion that sen-

[46] See 21 CFR 146.10 and 147.2(b).

sitivity disks containing antibiotic substances are drugs, and is not attacking a regulation.

In any event, even if the Commissioner's administrative determination were applicable to Bacto-Unidisks, it could be attacked in this enforcement proceeding. It is true as stated by petitioner (Pet. Br. 9) that under 507 (f) and 701(f) judicial review may be obtained of an order issued pursuant to section 507(f). Although the Notice of Proposed Rule Making which originated the proceedings resulting in the order in question purported to be issued under Subsection (f) of section 507, the Notice was not authorized by that subsection since the Notice specifically stated it was made by the Commissioner "on his own initiative" (25 F.R. 3084). The Notice could therefore have been issued only under 507(a), which does not incorporate the provisions for judicial review contained in 701(f), as does section 507(f). Consequently, even persons marketing disks to which the regulations apply had no right to seek review in a Court of Appeals.[47]

Moreover, collateral attack upon administrative determinations is barred only if the statutory remedy of judicial review is exclusive. Thus, even if the procedures under section 701 were available to respondent, section 701 (f) (6) provides that the remedies under 701 "shall be in addition to and not in substitution for any other remedies provided by law." In a recent decision, this Court rejected the Government's attempt to narrowly construe section 701 (f) (6), stating that the clause should be taken "at its face value" and read "in harmony with the policy favoring judicial review expressed in the Administrative

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[47] Statutory authorization is, of course, required for direct appeals from administrative decisions to Courts of Appeals.

Procedure Act and this Court's decisions" *Abbott Laboratories* v. *Gardner*, 387 U.S. 136, 146.

The fact that the Secretary's (Commissioner's) interpretation of the statute extending its coverage to sensitivity disks, was made in a rule-making proceeding, endows it with no aura of sanctity. The interpretation was just like any other statutory interpretation by an administrative official. As stated by the Court of Appeals below, the function of the reviewing court in this case ". . . is not to review the validity of the regulations to determine if they are supportable by substantial record evidence and not an abuse of administrative discretion, but to determine, based upon an interpretation of the statutory definition of a drug, whether the seized article is within the administrator's jurisdiction" (App. 202).

CONCLUSION

For the reasons stated, it is respectfully submitted that the decisions below were clearly correct and that the judgment of the court of appeals should be affirmed.

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No. 343

IN THE

Supreme Court of the United States

OCTOBER TERM, 1968

UNITED STATES,

Petitioner,

v.

AN ARTICLE OF DRUG * * * BACTO-UNIDISK * * *

Petition of Respondent Difco Laboratories, Inc. for Rehearing of Decision Reversing Judgment of the United States Court of Appeals for the Sixth Circuit

---

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Petition of Respondent Difco Laboratories, Inc. for Rehearing of Decision Reversing Judgment of the United States Court of Appeals for the Sixth Circuit

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Respondent Difco Laboratories, Inc. petitions this Court for rehearing of its decision of April 28, 1969, reversing the judgment of the United States Court of Appeals for the Sixth Circuit that the article Bacto-Unidisk is not a "drug" and, upon such rehearing, for affirmance of the judgment of the Court of Appeals.

REASONS FOR GRANTING REHEARING AND AFFIRMING THE JUDGMENT OF THE COURT OF APPEALS

It is apparent that there are a number of basic and critical aspects of the facts and the law of this case which have been overlooked and others which have been misunderstood, by the Court. This is clear from the lengthy

questioning by justices during the oral argument and more significantly, from the opinion of the Court itself. The important oversights and misunderstandings which constitute the reason for our request for a further hearing, are set forth hereinafter.

I. The sensitivity test, of which the disk is an element, is not used in diagnosis. There can be no reasonable question on this point. "Diagnosis" is recognition of a disease or illness. A disease cannot be recognized on the basis of the information derived from the sensitivity test since the test does *not* identify the organism which caused the disease. Since the evidence showed and the District Court found that identification of the organism is a step *preliminary* to the sensitivity testing procedure (App. 118, 119; Finding of Fact Number 7, App. 193), there is no sound basis for the idea that the disk is used in diagnosis.

Consequently, the emphasis in the opinion of the Court upon the addition of the term "diagnosis" to the definition of "drug" in the 1938 Act (Opinion 11-12) does not support the conclusion that the disk is a "drug". Moreover, "diagnosis" is an essential element of "cure" or "mitigation" and articles used in diagnosis were therefore "drugs" under the 1906 Act. Barium sulfate, for example, was regarded as a medicine or drug at least as early as 1926 when it first appeared in the United States Pharmacopeia (Xth Revision).

II. The disk is not used in the treatment of the patient. The trial court, found, instead, that the information obtained from the test, of which the disk is but one part, is used by the physician as a guideline to treatment (Finding of Fact Number 8, App. 194).

Since there is not even a suggestion in the opinion of this Court that Findings Number 7 and 8 are clearly erroneous we are at a loss to understand how the conclusion could be reached that the disk is used either in diagnosis or treatment.

We stated in our brief (p. 38) that—

> "Even if the finding of the District Court that the term 'drug' is limited to substances administered or applied to patients were entirely ignored, we submit that the evidence shows that the disks are nevertheless not 'drugs' because they are not used in 'diagnosis' or 'treatment' . . .".

It is, therefore, not accurate to suggest that the status of the disk is dependent upon "the same two-step analysis relied on by the courts below" (Opinion pp. 8-9). This simplified approach ignores Findings 7 and 8 and the evidence that the disk is not used in "diagnosis" or "treatment". The "two-step analysis" must be put aside, regardless of its validity or invalidity where, as here, it has been shown by expert testimony that the disk is not used in "diagnosis" or "treatment". There is no basis for assuming that Congress used those medical terms of art any differently than they are used in medical science.

III. It is stated in the opinion that "viewing the structure, the legislative history, and the remedial nature of the Act, we think it plain that Congress intended to define 'drug' far more broadly than does the medical profession". (p. 9).

It is respectfully submitted that this statement is not supported by the legislative record cited in the opinion insofar, at least, as it applies to the only clause of the definition of drug (Section 201(g)(1)(B)) with which we are here concerned. The opinion (p. 11) cites the statement of Senator Copeland that—

> "The present law defines drugs as substances or mixtures of substances intended to be used for the cure, mitigation, or prevention of disease [Clause (B)]. This narrow definition permits escape from legal control of all therapeutic or curative devices like electric belts, for example. It also permits the escape of preparations which are intended to alter the struc-

> ture or some function of the body, as for example, preperations intended to reduce excessive weight. . ." (78 Cong. Rec. 8960 (1934)).".

The only avowed extension of the definition of drug, therefore, is to "preparations which are intended to alter the structure or some function of the body", an approach incorporated in Section 201(g)(1)(C) and *not* in Clause (B) of that section, which is the only provision pertinent here.

If, therefore, it be a fact that "Congress intended to define 'drug' far more broadly than does the medical profession," it is by virtue of clauses (C) (and perhaps (B)) of Section 201(g)(1) and not by virtue of Clause (B) with which we are here concerned. Congress' intention in this respect is, therefore, not relevant to the question of whether the disk is a "drug".

It is said in the opinion that—

> "If Congress had intended to limit the statutory definition to the medical one, it could have so stated explicitly, or simply have made reference to the official United States Pharmacopoeia (or the National Formulary), as it did in the first of the three subsections of Section 201(g)(1), and let the definition rest there". (p. 10)

It is again clear from this quotation that we have not been successful in our attempt to explain an important aspect of this matter. If the alternative suggested of referring to the official compendia had been followed, many hundreds of substances which are regarded as drugs by the medical profession would have been excluded from the coverage of the statute.

Neither the Pharmacopoeia nor the Formulary purport to include all drugs recognized as such by the medical profession. Even new drugs cleared as safe and efficacious for use under Section 507 of the Food, Drug, and Cosmetic Act are not admitted to the official compendia until

the Committees on Admissions are satisfied of their therapeutic usefulness. It is apparent, therefore, that in order to extend the statute to all articles recognized as drugs by the medical profession Congress was required to go further than a reference to the official compendia and it did so, both in the 1906 and the 1938 Acts.

IV. It is stated in the opinion that "the parties do not disagree here, that a literal reading of the words 'intended for use in the . . . cure, mitigation, [or] treatment' of disease 'clearly has application' to the Bacto-Unidisk . . ." and that "Thus, the essential question for our determination is whether Congress intended the definition of drug to have the broad coverage the Courts below and the parties agree its words allow" (p. 9).

Respondent did not and does not agree to this proposition. This is made clear in our brief (pp. 33 et seq.). The District Court's findings and conclusion of Law Number 4 are inconsistent with it.* Findings Number 7 and 8 clearly exclude the application of "diagnosis" and "treatment" to the disk and they are not subject to modification by a preceding memorandum opinion.

V. The opinion states that—

> "Thus, it is clear that two parallel definitions [of 'drug' and 'device'] were provided for semantic reasons only . . . . No practical significance to the distinction between the two words arose until the pre-market clearance provisions, similar to the certification regulations for antibiotics enacted in 1945, were added after a drug tragedy in the fall of 1937." (p. 14).

An examination of the provisions of S. 5 (75th Congress), to which the new drug pre-clearance provisions

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* Conclusion of Law Number 4: "The seized article does not purport to be nor is it represented to be a drug within the meaning of 21 U.S.C. 321(g). It is not intended for drug use (see Findings Numbers 9 and 10) and it is the intended use which determines its status under that Section . . ."

were added, and of the Act as enacted in 1938, shows that this statement is far from accurate. The following provisions of S. 5 and the 1938 Act were then and are now applicable to drugs and *not to devices*: ** Sections 501 (a) (3), 501(a) (4), 501(b) and 501(d) relating to adulteration of drugs and Sections 502(e), 502(g), 502 (h), and 502(i), relating to misbranding of drugs.

These are and were important provisions of S. 5 and of the statute as enacted in 1938, which are of practical and serious legal significance to the distinction between the two words "drug" and "device". Others have been enacted since which strongly emphasize this significance.

It was pointed out in our brief (pp. 31-33), that the public health argument of the Government would result in application of the definition of "drug" to any article, including devices, where, in the opinion of the Food and Drug Administration, the more restrictive requirements of the statute relating to drugs, new drugs, and antibiotic drugs would offer greater protection to the public than those provisions relating to devices; that, since this approach offers no standard for determining the limits of the scope of the definition of "drug" the marketer of drugs and devices cannot know in advance how to avoid an unlawful course of action; and that to leave to conjecture the distinction between "drug" and "device" in a liability-without-fault criminal statute such as the Federal Food, Drug and Cosmetic Act would result in an unconstitutionally vague application of the statute within the meaning of *M. Kraus and Bros. Inc.* v. *United States*, 327 U.S. 614, 621-622 (1946).

The argument is pointed up by the many critical provisions of the statute, above listed in part, which are brought into play when the Food and Drug Administration regards an article as a "drug" but which are not operative if the article is a "device". If the marketer

** Dunn, Federal Food, Drug and Cosmetic Act, 970, 980-982.

decides that such a product is a device and the agency decides that it is a drug, the marketer may be subjected to criminal prosecution on at least five counts and, if convicted, to imprisonment for one year or a fine of $1,000 or both such imprisonment and fine (Section 303(a)). This result would follow regardless of any "consciousness of wrongdoing" (*United States* v. *Dotterweich*, 320 U.S. 277, 284 (1943)).

Finally, the examples of some of the products held to be devices by the Food and Drug Administration and the courts are so far removed from the mere mechanical type of device referred to in the opinion of the Court that one attempting to determine in which category the agency would classify a given product would be totally at a loss to decide upon which course of action to pursue. Two of the examples cited in our brief are of products which are notably similar to sensitivity disks, since they involve the use of the patient's urine or blood (Respondent's Brief pp. 48-40). There are many products heretofore regarded by the Courts and the Food and Drug Administration as "devices" which do not fall within the rigid classification made in the Court's opinion.

VI. It is fully evident as is shown by the history of the certification regulations applicable to sensitivity disks, by the proceedings in the District Court, and by the brief and argument of the Government in the Court of Appeals and in this Court, that the principal reliance of the Government in this case has been upon the allegation of danger to public health from the results of a sensitivity test in which a faulty disk was used. The Government failed to support this allegation either at the trial or in this Court, but the Court has accepted it as a determining factor in this case.

The opinion states that—

> "It is enough for us that the expert agency charged with the enforcement of remedial legislation has determined that such regulation is desirable for the

public health, for we are hardly qualified to second-guess the Secretary's medical judgment" (p. 8).

It is submitted that the only reason for relying upon the agency's judgment concerning the public health matter would be to show the existence of a remedial purpose which would justify the extension of the definition of "drug" beyond the meaning of Clause (B) of the definition (Section 201(g)(1)) as established by the evidence at the trial and the findings of fact of the lower Court. In fact, there is no other apparent reason for even referring to that judgment of the Secretary.

This seems evident from those portions of the Court's opinion invoking the purpose of the Act of protecting the public health (p. 15, preceding "IV") and the expressions of apprehension that an exclusion of discs from the definition of "drug" "might undercut the value of testing the antibiotics themselves, for such testing would be a useless exercise if the wrong drug were ultimately administered, even partially as the result of an unreliable disk" (p. 16). The opinion thus evokes the public health claim of the Government as a prime basis for reversal of the decisions of the lower courts.

This approach by the Court has been traditional in cases where it was apparent that the element of protection of the public health was involved, as in *Sullivan* * and *Dotterweich* ** cited on page 15 of this Court's opinion. In both of those cases there was no issue as to whether the articles involved were drugs. Consequently, the question of the relation of the public health to the regulation of such drugs was not in issue (as it now is here).

The regulations in connection with which the judgment of the agency was made were not subject to the public hearing procedures of the Act, as are some regulations

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* *United States* v. *Sullivan*, 332 U.S. 689 (1948).

** *United States* v. *Dotterweich*, 320 U.S. 277 (1943).

thereunder, nor is the judgment upon which they are based conclusive upon the Courts. This was recognized and noted by the Court of Appeals (App. 202).

With all of these factors in mind we must conclude that the Court's view that the judgment of the Secretary on this prime issue should not be disturbed or "second-guessed", deprives respondent of any real hearing in this matter, for, despite its constant emphasis upon this issue, and the prominence which it has received, the government is protected from all questioning of the validity of the Secretary's (Commissioner's) judgment by this Court's ruling.

Once the regulations extending the definition of "drug" to sensitivity disks were issued and were challenged in the seizure proceeding in the District Court, the only forum available either to the Government or claimant-respondent to support or challenge the basis for the regulations—their alleged desirability for protection of the public health—was by evidence at the trial on the question of whether, because of the public health issue, the remedial purpose of the statute could be invoked to justify a construction of Clause (B) of Section 201(g)(1) which goes beyond its meaning in medical science.

The refusal to consider such evidence and the acceptance of the agency's judgment without critical examination of it on the basis of the facts precludes respondent from the opportunity of defending itself to which it is entitled. We earnestly appeal to the Court to reconsider this decision in the light of the evidence of record, the literature cited by the Government itself in this Court, and the salient fact that throughout the pertinent time-periods the Government has been unable to produce a single instance of harm to a patient or even of a test report misleading to a physician, which was caused by a faulty disk. This, despite the fact that sensitivity disks have been marketed commercially for some 18 or 19 years of which about 12 or 13 were before the certification regulations were issued.

VII. It is shown in respondent's brief (pp. 44-47) that, even if the Bacto-Unidisk is a drug it is not subject to certification because it is fully clear from the legislative history that only antibiotic drugs intended for administration or application to patients were ever intended by the Congress to be certified. As the brief shows, the Department of Health, Education and Welfare itself has recognized that the purpose of the certification provisions of the Act (Section 507) is to subject antibiotic drugs *to be administered to human beings* to batch certification. This purpose obviously does not include sensitivity disks.

It is submitted that this limitation of Section 507 should, itself, require affirmance of the decision of the Court of Appeals. The opinion does not indicate whether the point was considered by this Court.

VIII. There are thousands of laboratory reagents such as the Bacto-Unidisk which are used to make tests indirectly related to the practice of medicine in the sense that the information obtained from such tests is used in one way or another to aid the physician. No person and no organization knows how many of these thousands of products fall within the category of "drugs" under the decision of the Court in this case.

As stated in respondent's brief—

> "There are more than 150 pages in the United States Pharmacopeia (and others in the National Formulary) describing hundreds of laboratory reagents or testing materials for use in making the various tests and assays described in the Pharmacopeia" (p. 37).

The reagents so listed, which are only a few of those now in use, are not regarded as drugs by the Committees on Revision of the official compendia and therefore do not appear in the monograph sections of the compendia. Thus, they are not "recognized" in the sense of Section 201(g)(1)(A) (App. 153-154; 155-157; 160-167).

It is to be anticipated that, under the decision of this Court, a large proportion—perhaps most of those classified as drugs—would be regarded as new drugs and therefore subject to the pre-clearance procedures requiring a showing of safety and effectiveness under Section 505 of the Act. This is because many of these products are either entirely new or are improvements upon predecessor products. The volume of business in these reagents is, in many if not most instances, of such a low order that the ability of manufacturers to continue their production would be questionable in the face of the high expense and the long periods of time required for industry to obtain the necessary evidence to support, and for the Food and Drug Administration to process, a new drug application.

We want to emphasize this point: these thousands of products (some companies manufacture and market as many as 7,000 or more) are not distributed through drug channels and are handled, not by medical supply houses, but by general laboratory supply companies.

It is fully apparent to the affected industry that, if laboratory reagents are to be controlled by a regulatory agency, they must be classified as devices (where, as here, they lend themselves to such a classification) or an entirely new system of regulation must be devised by the Congress. These products simply do not lend themselves to control as "drugs". For example, the Prescription Drug Amendment (Section 503 of the Act) obviously is inapplicable because laboratory reagents never come into the hands of patients; and, if an article such as the Bacto-Unidisk is indeed a drug, it could be labeled "for use in the treatment of bacterial infections"—obviously a false claim. If they are not classified as "devices" and no new regulatory system is provided, confusion and uncertainty and the loss by laboratories of testing tools which are of benefit to the physician in his practice, will inevitably result.

These problems have patently not been given serious consideration by the Food and Drug Administration. The inability of the marketer of laboratory reagents to tell whether his products are "drugs" has been markedly increased by the decision of this Court and the regulatory agency is now free to pick and choose which reagents it will regulate as drugs and which it will ignore.

It is submitted that, where so many thousands of "little" products are concerned the situation with which those who market them are faced is unhealthy and unwarranted.

CONCLUSION

It is respectfully submitted that rehearing of this matter should be granted and that the decision of the Court of Appeals should be affirmed.

Respectfully submitted,

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CERTIFICATE OF COUNSEL

I hereby certify that the foregoing petition for rehearing is presented in good faith and not for delay.

EDWARD BROWN WILLIAMS

May, 1969

SUPREME COURT OF THE UNITED STATES

No. 343.—October Term, 1968.

United States, Petitioner, v. An Article of Drug . . . Bacto-Unidisk . . .	On Writ of Certiorari to the United States Court of Appeals for the Sixth Circuit.

[April 28, 1969.]

Mr. Chief Justice Warren delivered the opinion of the court.

At issue here is the scope of the statutory definition of drug contained in the Federal Food, Drug, and Cosmetic Act and the extent of the Secretary of Health, Education, and Welfare's regulatory authority under that definition. The specific item involved in this definitional controversy is a laboratory aid known as an antibiotic sensitivity disc, used as a screening test for help in determining the proper antibiotic drug to administer patients. If the article is a "drug" within the general definition of § 201 of the Federal Food, Drug, and Cosmetic Act (21 U. S. C. (Supp. II) § 321), then the Secretary can subject it to pre-market clearance regulations promulgated pursuant to § 507 of the Act (21 U. S. C. § 357). Section 507 authorizes the Secretary to require batch certification of any antibiotic product which also meets the general drug definition of § 201. If, on the other hand, the article is merely a "device" under the Act, it is subject only to the misbranding and adulteration proscriptions of the Act and does not have to be pre-tested before marketing; and, of course, if the disc does not fall under either definition, the Act itself is totally inapplicable.

When the respondent marketed its discs without complying with the certification regulations of the Secretary, the Government condemned them pursuant to § 301 of

the Act on the assumption that the discs were drugs and thus validly subject to pre-market regulation. In this action following the condemnation, however, the United States District Court for the Eastern District of Michigan held that the discs were not drugs within the meaning of the Act, suggesting that, if anything, they were devices. It therefore ruled that, since pre-market clearance was not required or authorized, the seizure was improper. The Court of Appeals for the Sixth Circuit affirmed on the same reasoning. We reverse.

I.

Some background information about the development of the discs and the controlling legislation is necessary for an understanding of the determinations made by the Secretary and the courts below. Various antibiotics, known more commonly as "wonder drugs" under such familiar names as penicillin, aureomycin, terrecyclin, tetracyclin, and streptomycin, have proved very useful since World War II in treating numerous infectious diseases.[1] Produced biologically, however, these drugs tend to vary greatly in their quality and potency unless developed, and thereafter tested, under very carefully controlled conditions. Consequently,[2] Congress enacted

[1] See generally, Goodman & Gilman, The Pharmacological Basis of Therapeutics, 3d ed., 1965.

[2] See H. R. Rep. No. 702, 79th Cong., 1st Sess. (1945). Section 507 (21 U. S. C. § 357) reads as follows:

"(a) The Secretary of Health, Education, and Welfare, pursuant to regulations promulgated by him, shall provide for the certification of batches of drugs composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other antibiotic drug, or any derivative thereof. A batch of any such drug shall be certified if such drug has such characteristics of identity and such batch has such characteristics of strength, quality, and purity, as the Secretary prescribes in such regulations as necessary to adequately insure safety and efficacy

§ 507 of the Food, Drug, and Cosmetic Act, directing the Secretary of Health, Education, and Welfare to promulgate regulations establishing such standards of identity, potency, quality, and purity as necessary to ensure the "safety" and "efficacy" of those antibiotics. At present, more than 30 antibiotic drugs are listed (21 CFR § 145.3) with accompanying regulations covering more than 700 pages in the Code of Federal Regulations (21 CFR §§ 141.1–148z.4).

With the proliferation of the various types of antibiotics, doctors found a need for a screening test to help choose which antibiotic to use in treating a particular infection. A diffusion test, using antibiotic sensitivity discs like the one in question here, soon became a widely

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of use, but shall not otherwise be certified. Prior to the effective date of such regulations the Secretary, in lieu of certification, shall issue a release for any batch which, in his judgment, may be released without risk as to the safety and efficacy of its use. Such release shall prescribe the date of its expiration and other conditions under which it shall cease to be effective as to such batch and as to portions thereof. For purposes of this section and of section 502 (1), the term 'antibiotic drug' means any drug intended for use by man containing any quantity of any chemical substance which is produced by . . . microorganism and which has the capacity to inhibit or destroy microorganisms in dilute solution (including the chemically synthesized equivalent of any such substance).

"(b) Regulations providing for such certifications shall contain such provisions as are necessary to carry out the purposes of this section, including provisions prescribing (1) standards of identity and of strength, quality, and purity; (2) tests and methods of assay to determine compliance with such standards; (3) effective periods for certificates, and other conditions under which they shall cease to be effective as to certified batches and as to portions thereof; (4) administration and procedure; and (5) such fees, specified in such regulations, as are necessary to provide, equip, and maintain an adequate certification service. Such regulations shall prescribe only such tests and methods of assay as will provide for certification or rejection within the shortest time consistent with the purposes of this section."

employed screening method.[3] In this test, a round paper disc, which has been impregnated with a specific antibiotic, is placed in contact with sample cultures, or isolates, of a patent's virus, grown in a special culture medium (agar) from a specimen of the patient's fluid (blood, spinal fluid, sputum, urine, etc.). In those places impregnated with an antibiotic to which the patient's infection is sensitive, no new isolate will grow, leaving a clear area (an "inhibition zone"); in those places impregnated with a drug to which the infection is resistant, the isolate will grow, leaving no clear area. The disc is used, in conjunction with a patient's specimen, in laboratory work exclusively, and never comes in contact with any part of the patient's body itself.

The discs had been in general use for some four years when, in 1960, the Secretary of Health, Education, and Welfare determined to regulate them pursuant to § 507. After notice and an opportunity for public participation, the Commissioner of Food and Drugs, under authority delegated by the Secretary, promulgated regulations requiring pre-clearance, batch-testing, and certification of antibiotic sensitivity discs (25 Fed. Reg. 9369). The Commissioner's action, the regulations noted, followed "numerous complaints by the medical profession, hospitals, and laboratory technicians" and a resulting extensive survey of the use of the discs. That study found the discs unreliable in their statements of potency with

[3] See generally, Bauer, Kirby, Sherris, and Turck, Antibiotic Susceptibility Testing by a Standardized Single Disk Method, 45 American Journal of Clinical Pathology 493 (1966); Petersdorf and Sherris, Methods and Significance of In Vitro Testing of Bacterial Sensitivity to Drugs, 39 American Journal of Medicine 766 (1965); Gould, The Laboratory Control of Antibiotic Therapy, 3 Chemotherapia 477 (1961); Second Report of the Expert Committee on Antibiotics, Standardization of Methods for Conducting Microbic Sensitivity Tests, World Health Organization Technical Report Series No. 210, pp. 12–17 (1961).

resulting loss of safety and efficacy, and thus found it "vital for the protection of public health" to adopt the regulations (25 Fed. Reg. 9370).

This case arose in May 1962 as an *in rem* seizure proceeding against an interstate shipment of a number of cases of sensitivity discs, manufactured by respondent Difco Laboratories, Inc., under the trade name of "Bacto-Unidisk." In condemning the product pursuant to § 301 *et seq.* of the Food, Drug, and Cosmetic Act, the United States claimed, *inter alia*, that the product, as a "drug" within the meaning of the Act, had not been certified nor exempted from certification as required by § 507 (21 U. S. C. § 357) and the regulations thereunder and was therefore misbranded under § 502 (21 U. S. C. § 352).[4] The seizure was proper only if the Secretary's regulations subjecting the discs to the pre-market clearance requirements were authorized by the Act. Since the scope of the Secretary's pre-market regulatory power over antibiotic drugs under § 507 depends ultimately on the Act's general definition of "drug" in § 201 (g), the validity of the disc regulations respondent allegedly violated turned on the coverage of the drug definition:

"For the purposes of this Act—

. . . . . .

"(g)(1) The term 'drug' means (A) articles recognized in the official United States Pharmacopoeia,

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[4] Section 502 (21 U. S. C. § 352) reads, in part, as follows:

"A drug or device shall be deemed to be misbranded—

"(1) If it is, or purports to be, or is represented as a drug composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other antibiotic drug, or any derivative thereof, unless (1) it is from a batch with respect to which a certificate or release has been issued pursuant to section 507, and (2) such certificate or release is in effect with respect to such drug: *Provided*, that this paragraph shall not apply to any drug or class of drugs exempted by regulations promulgated under section 507 (c) or (d)."

official Homoepathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C); but does not include devices or their components, parts or accessories."

If, on the other hand, the product was a "device," only the misbranding, adulteration, and labeling provisions of §§ 501 and 502 applied, and the Secretary's disc certification regulations were invalidly promulgated. Although a "device" expressly cannot be a "drug" under the last sentence of the drug definition above, a device is given almost a parallel definition in § 201 (h):

"The term 'device' . . . means instruments, apparatus, and contrivances, including their components, parts and accessories, intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; or (2) to affect the structure or any function of the body of man or other animals."

Finally, it was established at trial that of the various definitions given above, the operative ones in this case were § 201 (g)(1)(B) of the drug provision and § 201 (h)(1) of the parallel device definition;[5] the essential question underlying the validity of the regulations, then, was whether the Bacto-Unidisks were "articles intended

[5] Respondent's witnesses established that sensitivity discs are not listed in the United States Pharmacopoeia or the National Formulary, and thus do not come within that portion of the definition of "drug" in § 201 (g)(1)(A).

for the use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals."

In resolving this question in the negative and holding the seizure invalid, the District Court noted in a memorandum opinion[6] that the concept of drug is limited in a medical sense to articles administered to man either externally or internally, and ruled that the "evidence affords no basis for the conclusion that the definition of 'drug' in the Federal Food, Drug, and Cosmetic Act was intended by Congress to extend beyond the meaning of that term in medical science, to encompass these sensitivity discs." The District Court pointed out that although a "literal reading" of § 201 (g)(1)(B) "clearly has application to the article libeled herein," enforcing such an application would be "ridiculous and contrary to common sense." The court therefore held that the Bacto-Unidisk did not fall within the purview of the Act for the reason that it was not medically a drug, and suggested, without deciding, that the discs would be more appropriately classified as "devices" under the Act.

On appeal, the Court of Appeals for the Sixth Circuit affirmed, accepting the District Court's conclusions that the Bacto-Unidisk was not a "drug" in the medical sense of the term and that Congress did not intend the statutory definition of "drug" to be any broader than the medical one. 392 F. 2d 21, 23. The court noted that the discs did aid physicians in the determination of what antibiotic to use for the cure, mitigation, or treatment of disease by furnishing useful information, but held that Congress did not intend to apply the statutory phrase "intended for the use in the . . . cure, mitigation, [or] treatment" in such an indirect manner. 392 F. 2d 21, 22. We granted the Government's petition for certiorari because this interpretation of the Act raised

[6] The District Court's opinion is unreported; its pertinent findings of fact and conclusions of law are quoted in the opinion of the Court of Appeals, 392 F. 2d 21, 22–23 (1968).

issues of importance in the administration of the Federal Food, Drug, and Cosmetic Act (393 U. S. 911 (1968)).

II.

Although there was some testimony below debating the precise extent of the public health dangers posed by the sensitivity discs, the courts below declined to substitute their judgment for that of the Commissioner of Food and Drugs by determining whether his action was really necessary to protect the public health from a purely medical viewpoint. Rather, the courts below quite properly confined the inquiry to an examination of whether the disc regulations, even if medically unwise, were authorized by the Act, and more specifically, by the Act's definition of "drug." Despite the renewed effort here to relitigate the public health issue, we agree with the decision implicitly made by the courts below not to base a resolution of this case on the public need for, or medical wisdom of, the Secretary's regulations requiring pre-market clearance of antibiotic sensitivity discs. It is enough for us that the expert agency charged with the enforcement of remedial legislation has determined that such regulation is desirable for the public health, for we are hardly qualified to second-guess the Secretary's medical judgment. Our sole concern is whether the statute's definition of "drug" authorizes the disc regulations contested here; and while we agree with the lower courts' limited conception of the issue, for reasons outlined below, we reverse their disposition of it.

Respondent's primary contention here is that the sensitivity discs are not subject to any of the provisions of the Act because Congress did not intend it to cover articles used so *indirectly* in the "cure, mitigation, and treatment" of disease. Respondent uses the same two-step analysis relied on by the courts below: (1) Congress did not intend to write the drug definition more broadly

than does the medical profession, and (2) the medical concept of drug is limited to articles that are administered to man either internally or externally. Alternatively, respondent argues, even if the Act's "intended for use" language does cover the discs, they must clearly be classified as devices. In view of the legislative history discussed below and the broad, remedial purpose of the Act itself, however, we hesitate to give the critical language such a narrow, restrictive reading in the absence of congressional direction to do so, and we therefore reject the contention that the discs do not properly fall within the purview of the Act. For the same basic reasons, we furthermore reject the argument that the discs, once found to come under the Act's coverage, must be classified specifically as devices and not drugs.

We need not stop to parse the language of the Act's definition of drug, for the District Court found, and the parties do not disagree here, that a literal reading of the words "intended for use in the . . . cure, mitigation, [or] treatment" of disease "clearly has application" to the Bacto-Unidisk. Although respondent again urges that the disk itself does not "treat" a patient in the same way an antibiotic does in terms of personal application, the disc plays at least some role in the selection of the appropriate drug. Thus, the essential question for our determination is whether Congress intended the definition of drug to have the broad coverage the courts below and the parties agree its words allow. Viewing the structure, the legislative history, and the remedial nature of the Act, we think it plain that Congress intended to define "drug" far more broadly than does the medical profession. The reason for including a separate, almost parallel definition of "devices" in the Act is, as the legislative history shows, relevant to congressional intent. It is therefore helpful to consider both the question of the Act's initial application and the question of the drug-device dichotomy at the same time.

III.

At the outset, it is clear from § 201 that the word "drug" is a term of art for the purposes of the Act, encompassing far more than the strict medical definition of that word. If Congress had intended to limit the statutory definition to the medical one, it could have so stated explicitly, or simply have made reference to the official United States Pharmacopoeia (or the National Formulary), as it did in the first of the three subsections of § 201 (g)(1), and let the definition rest there. The historical expansion of the statute's definition, furthermore, clearly points out Congress' intention of going beyond the medical usage. The 1906 Food and Drug Act, for instance, defined "drug" in a rather limited way to include "all medicines and preparations recognized in the United States Pharmacopoeia or National Formulary for internal or external use, and any substances or mixture of substances intended to be used for the cure, mitigation or prevention of disease of either man or other animals." 34 Stat. 768, 769. As subsequent congressional action clearly indicates, however, the scope of that original definition has since been greatly enlarged.

The enactment of the 1938 Federal Food, Drug, and Cosmetic Act illustrates the expansion of the definition of drug. One of the changes contemplated in S. 2800, an early version of the Act,[1] defined "drug" to include

"(1) all substances and preparations recognized in the United States Pharmacopoeia, Homoepathic

[1] The earliest versions were S. 1944, 73d Cong., 1st Sess. (1933), and S. 2000, 73d Cong., 2d Sess. (1934). S. 2800 was succeeded by S. 5, 74th Cong., 1st and 2d Sess. (1935–1936). S. 5 died in the House, but was succeeded by S. 5, 75th Cong., 1st and 3d Sess. (1937–1938), and was the bill eventually enacted into law, as supplemented by S. 3073, 75th Cong., 2d and 3d Sess., and H. R. 9341, 75th Cong., 3d Sess. (1937–1938).

Most of the Act's legislative history is reprinted in Dunn, Federal Food, Drug, and Cosmetic Act (1938).

> Pharmacopoeia of the United States or National Formulary or supplements thereto; and (2) all substances, preparations, and *devices* intended for use in the cure, mitigation, treatment, or prevention of disease in man or other animals; and (3) all substances and preparations, other than food, and all devices intended to affect the structure or any function of the body." (S. Rep. No. 493, 73d Cong. 2d Sess. (1934).) (Emphasis added.)

Senator Copeland of New York, who sponsored the Act, remarked about the inclusion of the word "devices" in his prepared statement introducing S. 2800 as follows:

> "The present law defines drugs as substances or mixtures of substances intended to be used for the cure, mitigation or prevention of disease. This narrow definition permits escape from legal control of all therapeutic or curative devices like electric belts, for example. It also permits the escape of preparations which are intended to alter the structure or some function of the body, as for example, preparations intended to reduce excessive weight. There are many worthless and some dangerous devices and preparations falling within these classifications. S. 2800 contains ample authority to control them." (78 Cong. Rec. 8960 (1934).)

The definition was revised in S. 5, 74th Cong., 1st and 2d Sess. (1935–1936), to include substances, preparations, and devices intended for *diagnostic* purposes, as well as for cure, mitigation, treatment, or prevention of disease (S. 5, § 201 (b), S. Rep. No. 361, 74th Cong., 1st Sess. (1935)).[8] As the inclusion of the word "diagnosis" came before the Senate for consideration, a controversy developed on the floor, aimed more at the word "devices,"

[8] See Dunn, *supra*, at 214, 237, 239.

which was not then before the Senate, than at the word "diagnosis." 79th Cong. Rec. 4841–4845 (1935).[9] Senator Clark contended that it was not proper to classify devices as drugs, and that diagnostic devices were so broadly defined as to make even a bathroom scale a drug:

> "If the devices ought to be outlawed, they ought to be outlawed, and I have no objection to that; but to maintain that a purely mechanical device is a drug and to be treated as a drug in law and in logic and in lexocagraphy is a palpable absurdity, in my opinion." *Id.*, at 4841.

In answer to Senator Clark's remark that a bathroom scale would be classified as a drug, Senator Copeland made the following comment:

> "Mr. President, I desire to state the effect of this amendment. There are on the market certain electrical devices. A man takes hold of the handles of a machine, and the indicator spins around. It stops at 'appendicitis' or it stops at 'meningitis'. . . . Such a device is manifestly a fraud upon society. That is what the amendment is designed to deal with." *Id.*, at 4842.

Despite Senator Copeland's proffered explanation, there was continued criticism during the Senate debates (79 Con. Rec. 4905–4920, 5215–5234)[10] of the definition on the grounds that it would lead to the incongruous result of calling the following items "drugs": shoulder braces (*id.*, at 4841), radium belts (*ibid.*), electrical devices (*id.*, at 4842), bathroom weight scales (*ibid.*), and hospital air conditioning apparatus (*id.*, at 5231).[11] The opposition finally settled on "crutches"

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[9] *Id.*, at 286–296.

[10] *Id.*, at 348–385, 429–476.

[11] *Id.*, at 429 (remarks of Senator Clark).

(*id.*, at 4913)[12] to signify the ultimate absurdity of the drug definition's broad coverage.

As a result of the criticism on the Senate floor, Senator Copeland proposed an amendment to add a definition of "device" to parallel that of drug, an amendment which was included [13] when the bill was returned to the Senate Committee on Commerce and later agreed to by the Senate without debate. (*Id.*, at 8351–8355.)[14] The ultimate effect of the various amendments, of course, was still to include devices under the control of the Act for the first time, the goal Senator Copeland had originally set out to achieve. As Congressman Chapman of Kentucky explained to the House after the bill had passed the Senate, "For the first time it is proposed in a bill before Congress to control therapeutic devices. . . . There are hundreds of worthless contrivances being sold and used by gullible people. Suffice it to say that a fake contraption for the cure of consumption is just as serious a menace to health as is a worhtless drug sold for the same disease." 80 Cong. Rec. 10,230, 10,231 (1936).[15] According to the Chief of the Food and Drug Administration, the reason for providing a separate definition of devices, instead of using Senator Copeland's original drug definition, was simply to avoid "the incongruity of classi-

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[12] *Id.*, at 369. Senator Bailey of North Carolina remarked:

"I do not think the President of the United States would tolerate for a moment a piece of legislation that described crutches as 'drugs' and advertising as 'adulteration,' carrying the English language very far."

[13] The substitute committee report noted only that "A definition of devices is provided paralleling that of drug. This expansion of the term 'drug' and the inclusion of devices are essential if the consumer is to be protected against a multiplicity of abuses not subject to the present law." (S. Rep. No. 646, 74th Cong., 1st Sess. (1935).) See Dunn, *supra*, at 477.

[14] *Id.*, at 495–496.

[15] *Id.*, at 571.

fying certain devices, such as the electric belt, therapeutic lamps, and so forth, as drugs. . . ." (Testimony given during hearings held on S. 5 by a House Subcommittee on Interstate and Foreign Commerce, 74th Cong., 1st Sess. (1935).)[16] Because of that incongruity as "pointed out by the Senate in the last consideration of the bill," the official explained, "they felt it proper to provide an independent definition of devices." Thus, it is clear that two parallel definitions were provided for semantic reasons only; for the purposes of the Act, the two definitions had the same effect of subjecting both drugs and devices to the adulteration and misbranding provisions. No practical significance to the distinction between the two words arose until the pre-market clearance provisions, similar to the certification regulations for antibiotics enacted in 1945, were added after a drug tragedy in the fall of 1937.[17] (S. 3073, 75th Cong., 2d and 3d Sess.). The excepting clause of § 201 (g)(1), stating clearly that a drug cannot be a device, was also added in 1938 (S. 5, 75th Cong., 3d Sess., S. Rep. No. 2139).

The historical expansion of the definition of drug, and the creation of a parallel concept of devices, clearly show, we think, that Congress fully intended that the Act's coverage be as broad as its literal language indicates—and equally clearly, broader than any strict medical definition might otherwise allow. Strong indications from legislative history that Congress intended the broad coverage the District Court thought "ridiculous" should itself satisfy us that the lower courts erred in

[16] *Id.*, at 1235, 1247.

[17] This was the "Elixir-Sulfanilamide" tragedy of September-October, 1937, where nearly 100 persons died as the result of consuming an untested drug. See Report of the Secretary of Agriculture on Deaths Due to Elixir Sulfanilamide-Massengill (submitted in response to S. Res. 194 of November 16, 1937), in Dunn, *supra*, at 1316–1327.

refusing to apply the Act's language as written. But we are all the more convinced that we must give effect to congressional intent in view of the well-accepted principle that remedial legislation such as the Food, Drug, and Cosmetic Act is to be given a liberal construction consistent with the Act's overriding purpose to protect the public health, and specifically, § 507's purpose to ensure that antibiotic products marketed serve the public with "efficacy" and "safety." Cf. *United States* v. *Sullivan*, 332 U. S. 689, 693–695 (1948); *United States* v. *Dotterweich*, 320 U. S. 277, 283–284 (1943).

IV.

Respondent's alternative contention, that even if its product does fall within the purview of the Act, it is plainly a "device" and therefore by definition necessarily not a "drug," must also be rejected, we believe, in light of the foregoing analysis. At the outset, it must be conceded that the language of the statute is of little assistance in determining precisely what differentiates a "drug" from a "device": to the extent that both are intended for use in the treatment, mitigation and cure of disease, the former is an "article" and the latter includes "instruments," "apparatus," and "contrivances." Despite the obvious areas of overlap in definition, we are not entirely without guidance in determining the propriety of the Secretary's decision below, given the overall goals of the Act and its legislative history.

More specifically, as we have previously held in an analogous situation where the statute's language seemed insufficiently precise, the "natural way" to draw the line "is in light of the statutory purpose" (*SEC* v. *Ralston Purina Co.*, 346 U. S. 119, 124–125 (1953)).[18] Since the

[18] Cf. *Cawley* v. *United States*, 272 F. 2d 443, 445 (C. A. 2d Cir. 1959): "[U]nless they explicitly forbid it, the purpose of a statutory provision is the best test of the meaning of the words chosen."

patient will tend to derive less benefit and perhaps some harm from a particular antibiotic if, though the drug itself was properly batch-tested, it was not the proper strain to use, it was entirely reasonable for the Secretary to determine that the discs, like the antibiotics they serve, are drugs and similarly subject to pre-clearance certification under § 507. An opposite conclusion might undercut the value of testing the antibiotics themselves, for such testing would be a useless exercise if the wrong drug were ultimately administered, even partially as the result of an unreliable disc.

Furthermore, the legislative history, read in light of the statute's remedial purpose, directs us to read the classification "drug" broadly, and to confine the device exception as nearly as is possible to the types of items Congress suggested in the debates,[19] such as electric belts, quack diagnostic scales, and therapeutic lamps, as well as bathroom weight scales, shoulder braces, air conditioning units, and crutches. In upholding the Secretary's determination here, without deciding the precise contours of the "device" classification, we need only point out that the exception was created primarily for the purpose of avoiding the semantic incongruity of classifying as drugs (1) certain quack contraptions and (2) basic aids used in the routine operation of a hospital—items characterized more by their purely mechanical nature than by the fact that they are composed of complex chemical compounds or biological substances. Finally, we are supported in the decision to uphold the FDA's determination that the sensitivity discs fall under the coverage of the Act and specifically under the drug provision thereof by the knowledge that the classification

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[19] Cf. *AMP, Inc.* v. *Gardner*, 389 F. 2d 825, 830 (C. A. 2d Cir.), cert. denied *sub nom.*, *AMP, Inc.* v. *Collin*, 393 U. S. 825 (1968), petition for rehearing pending.

of these discs as drugs may not be as contrary to common medical usage as the District Court and respondent would have us believe.[20]

In upholding the Secretary's construction of the Act, we are not unmindful of our warning that "In our anxiety to effectuate the congressional purpose of protecting the public, we must take care not to extend the scope of the statute beyond the point where Congress indicated it would stop." *62 Cases of Jam* v. *United States*, 340 U. S. 593, 600 (1951). Our holding here simply involves an obvious corollary to that principle, that we must take care not to narrow the coverage of a statute short of the point where Congress indicated it should extend.

Reversed.

MR. JUSTICE DOUGLAS, being of the view that an antibiotic sensitivity disc used by physicians to aid them in determining what antibiotic drug, if any, to give to a patient, is a "device" as defined in § 201 (b)* of the Act not a "drug" as defined in § 201 (g), would affirm the judgment.

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[20] See Dorland's Illustrated Medical Dictionary 449 (24th ed., 1965), where "drug" is defined as "Any chemical compound or any non-infectious biological substance, not used for its mechanical properties, which may be administered to or used on or for patients, either human or animal, as an aid in the diagnosis, treatment or prevention of disease or other abnormal condition, for the relief of pain or suffering, or to control, or improve any physiological or pathological condition."

* "The term 'device' . . . means instruments, apparatus and contrivances . . . for use in the diagnosis . . . of disease in man . . . ." It would indeed be difficult to write a clearer description of an antibiotic sensitivity disc.